DOCTOR OF PHILOSOPHY

# The Efficacy of Low-Level Laser Therapy Applied at Acupuncture Points in Knee Osteoarthritis
## a Randomised Double-Blind Controlled Trial

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2014


# THE EFFICACY OF LOW-LEVEL LASER THERAPY APPLIED AT ACUPUNCTURE POINTS IN KNEE OSTEOARTHRITIS: A RANDOMISED DOUBLE-BLIND CONTROLLED TRIAL

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# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| **AAOS:** | American Academy of Orthopaedic Surgeons |
| **ACL:** | Anterior cruciate ligament |
| **ACR:** | American College of Rheumatology |
| **AELs:** | Accessible Emission Levels |
| **ANSI:** | American National Standards Institute |
| **APs:** | Acupuncture points |
| **ATP:** | Adenosine Triphosphate |
| **BMI:** | Body mass index |
| **CAM:** | Complementary and alternative medicine |
| **CI:** | Confidence Interval |
| **cm:** | Centimetres |
| **$CO_2$:** | Carbon Dioxide |
| **CW:** | Continuous |
| **COX-2:** | Cyclooxygenase-2 |
| **DIQ:** | Disability Index Questionnaire |
| **DMTs:** | Diseases modifying treatments |
| **EA:** | Electo-acupuncture |
| **EBM:** | Evidence-based medicine |
| **EULAR:** | The European League Against Rheumatism |
| **FDA:** | Food and Drug Administration (USA) |
| **GaAlAs:** | Gallium-Aluminium-Arsenide |

| | |
|---|---|
| **GaAs:** | Gallium-Arsenide |
| **He-Ne:** | Helium-Neon |
| **HIV** | Human immune-deficiency virus infection |
| **Hz** | Hertz |
| **InGaAlP:** | Indium-Gallium-Aluminium-Phosphate |
| **IR:** | Infrared |
| **J:** | Joule |
| **J/cm$^2$:** | Joules per square centimetre |
| **KC:** | Knee circumference |
| **Kg:** | Kilogram |
| **KL:** | Kellgren and Lawrence grading scale |
| **KOA:** | Knee Osteoarthritis |
| **LASER:** | Light Amplification by Stimulated Emission of Radiation |
| **LLLT:** | Low-Level Laser Therapy |
| **MA:** | Manual acupuncture |
| **MASER:** | Microwave Amplification by Stimulated Emission of Radiation |
| **MHz:** | Mega Hertz |
| **Min:** | Minutes |
| **MJ:** | Milli Joules |
| **mm:** | Millimetres |
| **MRI:** | Magnetic Resonance Imaging |
| **mRNA:** | Messenger Ribonucleic Acid |
| **ms:** | Millisecond |
| **MTS** | Medial tenderness score |
| **mw:** | Milliwatts |
| **NdYAG:** | Neodymium-Yttrium-Aluminium-Garnet |
| **NIR** | Near infrared |

| | |
|---|---|
| **nm:** | Nanometres |
| **NO:** | Nitric Oxide |
| **NOS:** | Nitric Oxide Synthases |
| **NSAID:** | Non-steroidal Anti-inflammatory Drug |
| **OA:** | Osteoarthritis |
| **OARSI:** | The Osteoarthritis Research Society International |
| **PEDro:** | Physiotherapy evidence database |
| **PGE2:** | Prostaglandin E2 |
| **PPI:** | Present Pain Intensity |
| **PTD:** | Physiotherapy Department |
| **Quality of life:** | QoL |
| **RA:** | Rheumatoid Arthritis |
| **RCT:** | Randomised controlled trial |
| **RDBCT:** | Randomised, double-blind and placebo-controlled trial |
| **RSBCT:** | Randomised, single-blind and placebo-controlled trial |
| **REDOX:** | Reduction-Oxidation Reaction |
| **RNA:** | Ribonucleic acid |
| **RNS:** | Reactive Nitrogen Species |
| **ROM:** | Range of Motion |
| **ROS:** | Reactive Oxygen Species |
| **SD:** | Standard Deviation |
| **s:** | Second |
| **SFH:** | Security Forces Hospital |
| **SF-MPQ** | Short-Form McGill Pain Questionnaire |
| **SPSS:** | Statistical Package for the Social Sciences |
| **TCM:** | Traditional Chinese Medicine |
| **TENS:** | Transcutaneous electrical nerve stimulation |

| | |
|---|---|
| **TKA:** | Total knee arthroplasty |
| **TKR** | Total knee replacement |
| **UAV** | Univariate Analysis of Variance |
| **µm:** | Micrometers |
| **UK:** | United Kingdom |
| **USA:** | United States of America |
| **UV:** | Ultraviolet |
| **VAS:** | Visual analogue scale |
| **W:** | Watts |
| **WALT:** | World Association of Laser Therapy |
| **W/cm$^2$:** | Watt per centimetre square |
| **WHO:** | World Health Organization |
| **WOMAC:** | Western Ontario and McMaster Universities osteoarthritis index |

# DEDICATION

*I wish to dedicate this thesis to my beloved father (May Allah's mercy be upon him) who was always proud of me and so sadly, passed away before I finished upon this PhD journey, with all loving memories.*

*This thesis is also dedicated to my beloved mother, a source of encouragement and inspiration to me throughout my life. Also, my wife Maram, and my daughters Joud, Jouri and Cady, and my son Saleh, for all of their support, inspiration, and love.*

*Through our loyalty to each we become stronger,*

*We Stand Together.*

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# DECLARATION

I hereby declare that this dissertation entitled " The efficacy of low-level laser therapy applied at acupuncture point in knee osteoarthritis: a randomised, double-blind controlled trial." has been prepared by me under the direct guidance of Mr. Carlos Wigderowitz for the award of PhD Degree at the University of Dundee, Dundee, Scotland.

I have not submitted this dissertation previously for the award of any degree or diploma at any other institution.

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# ABSTRACT

**Background:** Osteoarthritis (OA) is the most common form of arthritis and is a major cause of disability and impaired quality of life (QoL). The prevalence of OA is rapidly increasing affecting approximately 15% of the world's population. Currently, there are no disease modifying treatments available. Non-steroidal anti-inflammatory drugs, the most widely prescribed medications for patients with knee OA (KOA), are associated with serious side effects, including bleeding and gastric ulceration. As a result, both patients and professional societies are looking for alternative therapies, with good effects, and less toxicity, to control pain sufficiently. Low-level laser therapy (LLLT) is a non-invasive treatment modality in the field of physiotherapy for pain management. Nonetheless, the effectiveness of LLLT in the treatment of OA is debatable.

**Objectives and Design:** A randomised, double-blind, controlled trial was conducted to evaluate the efficacy of LLLT when it is applied on specific acupuncture points (APs) at the knee joint in combination with exercises and advice in patients with KOA.

**Participants:** Forty-nine patients with KOA were randomly assigned into two groups; active laser group (n= 26) and placebo laser group (n= 23).

**Intervention:** Using a gallium-aluminium-arsenide laser device, patients received either active or placebo LLLT treatment at five APs (ST 35, Xiyan, ST 36, SP9, and SP10) on the affected knee. All participants received a series of 9 treatment sessions over a period of three weeks by using LLLT (active or placebo) in addition to strengthening exercise and advice.

**Outcome Measures:** Visual analogue scale (VAS), Saudi knee function scale (SKFS), active range of motion (ROM), knee circumference (KC), and patient satisfaction were

assessed at baseline, at the 5th treatment session, at the last (9th) treatment session, after six weeks and then six months after the last treatment session.

**Result:** There was a statistically (but not clinically) significant improvement in the laser group compared to the placebo group in the primary outcome VAS after six weeks (P= 0.014) and after six months of the last session of treatment (P= 0.003). There was a statistically (but not clinically) significant improvement in the laser group compared to the placebo group in the SKFS scores at the last treatment session (P= 0.035), and after six months (P= 0.006); in ROM only after six months (P= 0.019); in patient satisfaction at the 5th session (P= 0.033) and after six months. No significant difference between both groups was noted in the KC at any time. Within both groups there was statistically significant improvement in most outcomes.

**Conclusions:** The results demonstrate that the short-period application of LLLT on specific APs associated with exercises and advice is effective in reducing pain and improving the QoL in patients with KOA.

# Chapter 1 INTRODUCTION

## 1.1 Problem definition

Osteoarthritis (OA) is the most common form of arthritis, and is a major cause of disability and impaired quality of life (QoL) (Castaneda *et al.,* 2012; Le *et al.,* 2012). The direct cause of OA is unknown; however, it is a slowly progressive disease caused by various biological processes, such as wear and tear, inflammation, and enzymatic cartilage degradation on a joint (Breedveld 2004; Hellio Le Graverand-Gastineau 2009; Konttinen *et al.,* 2012). OA is common in the elderly, especially in females, but, it also affects younger people, especially in the obese populations (Schuelert *et al.,* 2011).

The prevalence of OA is rapidly increasing; it affects approximately 15% of the world's population (Egloff *et al.,* 2012). This prevalence might be attributed to the ageing population and an increase in the prevalence of obesity worldwide, as a risk factor for OA (Al-Arfaj 2003; Felson *et al.,* 2000; Le *et al.,* 2012; Breedveld 2004), in addition to sedentary lifestyles and injuries. In the United States (USA), OA is affecting approximately 14% of adults aged 25 and older, and 33.6% over the age of 65 (Lawrence *et al.,* 2008). By the year 2020, almost 60 million (18.2% of the population) Americans will be affected by arthritis (Lawrence *et al.,* 1998). Other estimates show that by 2030, 25% of the USA adults will suffer from arthritis (Hootman and Helmick, 2006). In the UK, it has been estimated that 40% of the population over the age of 65 have symptoms associated with knee or hip OA (Zhang *et al.,* 2008).

In Saudi Arabia, where the data collection of the current study was done, as in many other Arab countries, there are no accurate data to report the prevalence of OA. This does not imply that OA is less prevalent in these societies; Al-Arfaj and Al-Boukai (2002) concluded that radiographic evidence of knee OA (KOA) and its symptoms is more commonly found in the Saudi population than it is in western societies. Nevertheless, they reported that the incidence of KOA in Saudi Arabia is approaching 60.6% in the 66–75 years age-group, in some regions. In recent years, in Saudi Arabia,

and worldwide, the prevalence of OA is not limited to the elderly population, but it affects younger people also. Interestingly, in Saudi Arabia and other Gulf countries, adolescent overweight and obesity, as a prominent risk factor for OA, are among the highest in the world, while it reaches 8–9% in pre-school children (Ng *et al.,* 2011). It has been reported that becoming overweight earlier in adult life increases the risks of KOA (Dawson *et al.,* 2003; Holliday *et al.,* 2011). Therefore, it may not be surprising to see patients with KOA in their thirties or even younger, which makes OA an increasing concern.

Although OA may affect any synovial joint in the body, especially weight bearing joints, the knee is the most frequently affected joint (Coleman *et al.,* 2012; Gupta *et al.,* 2005). Not only is the articular cartilage affected by this condition, but all joint structures are involved, including the subchondral bone, ligaments, capsule, synovial membrane, menisci, and extra-articular muscles (Brandt *et al.,* 2006; Hellio Le Graverand-Gastineau, 2009).

Currently, there are no disease-modifying treatments (DMTs) that have been approved by the Food and Drug Administration (FDA) or European Medicines Agency for treating OA (Egloff *et al.,* 2012; Hellio Le Graverand-Gastineau, 2009; Schuelert *et al.,* 2011; Selvan *et al.,* 2012). Notwithstanding, there are large numbers of non-pharmacological therapies (physiotherapy, occupational therapy, weight loss, education, etc.), pharmacological therapies (e.g., simple analgesic, intra-articular injections, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)) and surgical therapies (e.g. total knee replacement (TKR) and osteotomies). These therapies are mostly symptomatic treatments. Therapeutic goals for treating patients with KOA focus on reducing joint pain, stiffness, and physical disability; improving joint mobility and health-related QoL; maintaining joints from further deterioration; and finally, educating patients regarding the nature of their problem and its management (Zhang *et al.,* 2008).

Unfortunately, NSAIDs, the most widely prescribed medications for patients with KOA, are associated with serious side effects, including bleeding, gastric ulceration, and increased risk of cardiovascular disease, such as myocardial infarction (McDonald and Walsh, 2012; Moodley 2008; Schuelert *et al.,* 2011). Furthermore, elderly patients suffering from OA are usually accompanied with several co-morbidities, including hypertension, cardiovascular disease, peripheral vascular disease, congestive heart failure, renal function impairment, diabetes, and respiratory disease, which increase the risk of drug-to-drug interactions (Breedveld, 2004; Hellio Le Graverand-Gastineau, 2009; Le *et al.,* 2012). Even more, these patients usually complain of moderate to severe pain which restricts their mobility, hastens disease progression, and exacerbates joint pain.

Moreover, surgery, as the last chance treatment, has its own side effects and limitations, such as infection, bleeding, and knee instability; in addition, many patients with co-morbidities are not fit to have surgery (Felson *et al.,* 2000; Ronn *et al.,* 2011). The socioeconomic impacts of OA are tremendous in terms of the costs associated with OA interventions and the management of its possible adverse effects. In addition there are the costs associated with surgery, long hospitalisation, clinical studies, and lost work productivity due to disability (Breedveld, 2004). Furthermore, according to Chen *et al.,* (2012), it has been found that OA costs the USA, Canada, the UK, France, and Australia between 1–2.5% of the gross national product (GNP) for those countries.

Last, but not least, it has been reported that older patients with OA may be more reluctant to seek medical help because of pessimism about the availability, effectiveness and risks of treatment (Sanders *et al.,* 2004).

Consequently, both patients and professional bodies are looking for cost-effective, low-toxicity alternative therapies to control pain. Non-pharmacological therapy as the first

line of treatment is often successful; although its beneficial effects may be limited in time, there are often little or no side effects, and patient satisfaction is usually relatively high (Pendleton *et al.,* 2000; Zhang *et al.,* 2008). Different modalities in physiotherapy, such as exercise, transcutaneous electrical nerve stimulation (TENS), acupuncture, and low-level laser therapy (LLLT) have been shown to help improve clinical symptoms and function of KOA, with fewer side effects than medical treatment (De Luigi, 2012).

LLLT is increasingly recognised as a non-invasive and safe treatment for numerous chronic conditions, including OA (Gur *et al.,* 2003a; Yurtkuran *et al.,* 2007). It has been reported by Tascioglu *et al.* (2012) that several studies showed that LLLT has anti-inflammatory, anti-oedema effects, and it has a role in pain reduction without any side effects. Although the results are conflicting, there is a large amount of research available on the subject of LLLT in treating acute and chronic painful conditions, such as fibromyalgia, rheumatoid arthritis, postoperative pain, low back pain, and OA (Gur *et al.,* 2003a). Similarly, the results of using LLLT on patients with KOA are conflicting. Although many studies showed significant improvements (Alfredo *et al.,* 2011; Fukuda *et al.,* 2011; Hegedus *et al.,* 2009; Rayegani *et al.,* 2012; Shen *et al.,* 2009; Stelian *et al.,* 1992), others did not (Bulow *et al.,* 1994; Tascioglu *et al.,* 2004; Trelles *et al.,* 1991, Yurtkuran *et al.,* 2007).

Acupuncture is among the non-pharmacological interventions, which have been introduced as a safe and relatively cost-effective therapy for patients with KOA (Berman *et al.,* 1999; Tillu *et al.,* 2002; Witt *et al.,* 2005). Berman *et al.,* (1999) reported that in many Asian countries, as in western countries, acupuncture is a popular treatment for arthritis. Stimulation of acupuncture points (APs) has been shown to be effective in relieving pain in many chronic cases, such as in KOA (Lu *et al.,* 2010; Tillu *et al.,* 2002). Stump and Roberts-Retzlaff (2006) stated that it has been reported that

laser light can evoke specific effects in the periphery of the nervous system and in the brain by stimulating APs.

Stimulation of APs by LLLT (laser acupuncture) has been in use since 1968 (Mester *et al.,* 1985). Despite that, the exact mechanism of pain reduction by both LLLT and acupuncture is not completely understood (Gur *et al.,* 2003a; Ahsin *et al.,* 2009). According to Baxter *et al.* (2008), LLLT has been recommended as an effective alternative to metal needles for stimulating APs. LLLT has some advantages over metal needles in acupuncture treatment, including that LLLT can be applied on anatomically dangerous areas (lung, heart, and neural and vascular structures) for relieving pain of surrounding tissues, while acupuncture can cause organ puncture or damage to these structures. LLLT can be applied to needle-phobic patients, burns or ulcerations, wounds, and implanted electrical device such as a pacemaker or medication pump. LLLT offers low cost, ease of application, and short time of application, and it is a non-invasive and safe treatment (e.g. in cases of human immunodeficiency virus infection (HIV) infection and hepatitis). Furthermore, LLLT has no heat or vibration, and is invisible above 770 nanometres (nm); hence, patients have difficulty knowing if they have received real treatment or not; in this respect, LLLT is superior to needles in studies using a blinding technique in randomised clinical trials (RCTs) (Baxter *et al.,* 2008; Relf *et al.,* 2008).

Recent studies have clearly shown that laser light can be successfully used for effective acupuncture treatment (Litscher and Opitz, 2012; Stump and Roberts-Retzlaff, 2006). Despite several studies that have been carried out to determine the efficacy of LLLT for treating KOA when it is applied at and around the knee joint (Alfredo *et al.,* 2011; Bulow *et al.,* 1994; Fukuda *et al.,* 2011; Gur *et al.,* 2003a; Hegedus *et al.,* 2009; Stelian *et al.,* 1992; Tascioglu *et al.,* 2004; Trelles *et al.,* 1991), studies concerning laser acupuncture are rare. To the best of the author's knowledge, to date, only two studies

have been published for testing the efficacy of LLLT when applied on APs in patients with KOA, and only one AP has been stimulated in each study (Shen *et al.,* 2009; Yurtkuran *et al.,* 2007).

The LLLT studies have been criticised because the laser devices, experimental designs, parameters, and techniques described in the literature are highly variable. Therefore, it is important to be careful when reviewing and comparing these studies. One more criticism has been noted by Brosseau *et al.,* (2004) in their systematic review, which is the lack of data on how LLLT effectiveness is affected by 4 important factors: wavelength, treatment duration, dosage, and site of application over nerves instead of joints. They recommended a need to investigate the effects of those 4 factors on the LLLT effectiveness for OA in RCTs.

## 1.2 Aim and hypothesis of the study

The aim of the current study is to assess the effects of LLLT as a non-invasive intervention for treating KOA, when applied in APs around the knee.

The null hypothesis of the study is that LLLT, applied to five APs around the knee in the treatment of KOA and in combination with a specific regimen of advice and exercise is not better than a placebo, applied with the same co-adjuvant therapeutic regimen.

## 1.3 Objectives of the study

In order to clarify the research question of the study, a randomised double-blind controlled trial (RDBCT) has been designed and executed to compare the two interventions.

The primary outcome of the RDBCT was pain relief at the 5th session, and 9th (final treatment session), at 6 weeks and at 6 months following the end of the intervention and as measured by VAS.

Secondary outcomes of the study were:

1. To evaluate QoL as measured by the Saudi Knee Function Scale (SKFS), a specific questionnaire designed to assess knee function, taking into account cultural characteristics.

2. To evaluate the effects of the LLLT treatment on the range of motion (ROM) of patients treated.

3. To evaluate the effects of the LLLT on swelling as determined by knee circumference.

4. To evaluate patient satisfaction with the LLLT treatment.

The secondary outcomes were measured at the same time points as the primary outcome.

## 1.4 Thesis structure

The current thesis consists of 8 chapters. Chapter 1 provides the background to the thesis, including the problem definition, aim, hypothesis and the objective of the study. Chapter 2 provides a background and literature review of OA and KOA in particular, as treatment of this pathology is the central objective of the project and the condition being addressed. Also, this chapter discusses definitions of the condition, main existing treatments, demographics and burden of disease.

Chapter 3 discusses the principles of LLLT, explaining its history, development and supporting basic science. It discusses issues such as laser physics, relevant parameters for clinical treatment and different types of laser currently available for medical treatments, with particular focus in the chosen technique of LLLT.

Chapter 4 discusses the principles and practice in acupuncture, how it has emerged from an ancient Chinese medicine, to current evidence of its efficacy, and different techniques, including the use of needles and Electro- Acupuncture (EA), which have been gaining increasing acceptance and which may help in the control of pain in patients with chronic diseases including KOA.

Chapter 5 explains in detail the methodology of the current study as a RDBCT, how the participants were recruited to the study, inclusion and exclusion criteria, study design, randomisation and blinding techniques used. In addition the measurement tools used are discussed, including evidence from the literature of their validity, reliability and repeatability. Furthermore, this chapter gives details about instruments used in the study such as the laser unit and its parameters, APs used in the current study, how they were located, how they were irradiated, and the reasons behind being chosen are discussed in details in this chapter. Also, treatment procedure and data collection are discussed in detail. At the end of this chapter, there is a clarification of statistical tests that were used to analyse the data derived from each variable, and also how the current study was powered.

Chapter 6 presents the results of analysed data derived from each variable. The first section presents baseline and demographic data, in addition to their between-group analysis. The second and third sections present the within and between group analysis of data derived from each variable of the study. Lastly, possible correlation and relationships of different variables of the study were analysed.

Chapter 7 discusses the results of the study and then compares this with other findings of related and similar studies; followed by chapter 8, which presents the conclusion of the current study in addition to a summary and implications for current and future research.

# Chapter 2 Review of the literature of knee osteoarthritis (KOA)

## 2.1 Background of OA

As the most common type of arthritis, OA is a major cause of disability and impaired QoL (Castaneda *et al.,* 2012; Le *et al.,* 2012). It is classified as one of the oldest known diseases on the planet, with evidence derived from paleopathological studies. It has been found in the skeletal remains of dinosaurs, in the spine of a 200 million year old Dimetrodon Permian reptile (Buchanan *et al.,* 2003), in Neanderthal and Cro-Magnon man (Dequeker and Luyten, 2008), in Saxons in England (Rogers *et al.,* 1981), in Egyptian mummies (Braunstein *et al.,* 1988), and in Icelandic Vikings (Byock *et al.,* 2005).

OA is characterised primarily by the degradation of the superficial cartilage layer. As the disease progresses, it spreads to the deeper layers of the cartilage, subchondral bone, and synovial membrane leading to increased friction between bones inducing pain and a progressing disability (Breedveld, 2004; Konttinen *et al.,* 2012). The direct cause of OA is unknown, particularly during the early phases of the disease (Breedveld 2004; Konttinen *et al.,* 2012). It was thought to be a result of simple wear and tear, but this idea was rejected, and a current model states that OA affects the whole joint as an organ, including cartilage, bone, synovium, muscles, and ligaments (Hellio Le Graverand-Gastineau, 2009; Pottie *et al.,* 2006). However, OA is a slowly progressive disease caused by various biological processes, such as wear and tear, inflammation, and enzymatic cartilage degradation on a joint (Breedveld 2004; Hellio Le Graverand-Gastineau, 2009; Konttinen *et al.,* 2012). OA is mainly characterised by different symptoms, such as joint pain, tenderness, stiffness, functional disability, joint instability, crepitus, occasional effusion, and limitation of movement.

## 2.2 Risk factors of OA

OA is a multifactorial disease associated with several risk factors, such as trauma, age, obesity, gender, overuse, and genetics. According to Felson (2013), these factors do not work alone to cause disease. For example, being an older overweight female when combined with a major injury presents a very high risk of KOA, whereas a younger overweight male person with a major injury has less risk of KOA.

Sarzi-Puttini *et al.,* (2005) divided the risk factors of OA into systemic (e.g. age, gender, ethnicity, and genetic), local biomechanical factors (e.g. joint injury, malalignment, overweight, and muscle weakness), metabolic and nutritional factors (e.g. vitamin D deficiency and hyperglycaemia). Another system classified the risk factors of KOA into nonmodifiable factors (e.g. age, gender, and genetic susceptibility/family history) and potentially modifiable factors (e.g. body mass index (BMI), occupational risk, joint injury, quadriceps weakness, nutrients, bone mineral density, and oestrogen deficiency). Zhang (2010) and Felson (2013) stated that recent reviews showed that major risk factors for KOA are older age, female gender, obesity, knee injury, and occupational overuse.

### 2.2.1 Age

OA has been found to be age-related (Felson 2004; Lawrence *et al.,* 2008). It affects the middle-aged and elderly, although it may be seen earlier in the younger population. Lawrence *et al.* (2008) estimated that 27 million US adults age 25 and older have clinical OA. However, the age of 45 is the most common age of onset of KOA (Buckwalter *et al.,* 2004). Therefore, it has been known to be a disease of middle age but its prevalence increases dramatically after this age. Woolf and Pfleger (2003) reported that radiographic studies of the USA and European countries showed that

populations aged ≥ 45 years have high prevalence rates of KOA. Furthermore, Felson (2004) stated that KOA is seen radiographically in 33% of the population older than 60 years of age. According to Chen *et al.* (2012), it has been shown that 15% of all musculoskeletal consultations were related to OA in those aged 45 and over, rising to 25% in those aged 75 and over.

With increasing age, the progress of OA starts with the failure of the cartilage collagen network, which ultimately becomes stiff, resulting in a decreased resistance of this network to mechanical failure (Verzijl *et al.,* 2002). Furthermore, with ageing, changes in articular cartilage accompanied with a decrease in joint proprioception and muscle strength or unstable articulation is likely to play a role in the progress of OA (Bosomworth, 2009; Felson *et al.,* 2000; Sharma *et al.,* 2003).

### 2.2.2 Gender and sex hormones

There is growing evidence that gender, especially combined with ageing, is a major predisposing factor of KOA in women (Chen *et al.,* 2012; Cho *et al.,* 2010; Coleman *et al.,* 2012; Egloff *et al.,* 2012; Lohmander *et al.,* 2004; Nishimura *et al.,* 2011). In their meta-analysis, Srikanth *et al.* (2005) found that females, particularly postmenopausal, tend to have a more severe KOA, which could be attributed to many factors. It could be attributed to the fact that the knee joint is controlled locally and systemically by different hormones, including sex hormones (oestrogens, androgens, and progesterone) (Boyan *et al.,* 2013). Moreover, there is increasing evidence that the oestrogen hormone has a role in maintaining the homeostasis of joint components including articular tissues (Roman-Blas *et al.,* 2009). Hence, hormonal changes in women around the time of menopause or postmenopause could contribute to KOA development and progression (Boyan *et al.,* 2013; Roman-Blas *et al.,* 2009). Interestingly, Carbone and his colleague

(2004) found that elderly women being treated with oestrogen had a significantly decreased prevalence of KOA. Furthermore, they stated that the majority of reports suggest a beneficial effect of oestrogen on OA.

Boyan *et al.* (2013), on the other hand, stated that OA is an inflammatory disease and older women tend to have more robust inflammatory and immune responses than men, therefore making them more likely to be affected by KOA, this may be due to development and persistence of inflammatory cytokines in the knee, which may be secondary to the influence of hormones. Furthermore, it has been suggested that men have mainly larger joint surfaces and hence higher cartilage volume than women, where a high volume of cartilage may be protective against OA (Cicuttini *et al.,* 2003; Eckstein and Wirth 2011). However, according to Eckstein and Wirth (2011), cartilage volume should not be directly compared according to gender.

### 2.2.3 Obesity and BMI

Numerous observational studies have identified obesity as a prominent risk factor for KOA (Dawson *et al.,* 2003; Manek *et al.,* 2003; Marks 2007; Toivanen *et al.,* 2010). The prevalence of obesity is increasing markedly worldwide, in the UK the percentage of prevalence of obesity increased between 1986 and 1993 from 6% to13% in men and from 8% to16% in women. Similar results have been noted in the USA; national population surveys obtained since 1960 until 1994 have reported that the prevalence of obesity has more than doubled from 12.8% to 27%, and nearly 61% of adults are overweight or obese. In Saudi Arabia, studies conducted from 1990 to 1993, have shown an overall prevalence of obesity of 22.1% and approximately 53% of Saudi adults are either overweight or obese (Al-Nozha *et al.,* 2005).

Individuals who were overweight earlier in adult life increase the risks of KOA (Dawson *et al.,* 2003; Holliday *et al.,* 2011). According to Rosemann *et al.* (2008), 3 to 6 times body weight is transferred across the knee joint during each step. In obese individuals, it would increase the stresses and strains in the knee joint, which increase joint loading and alterations in gait mechanics. However, increased joint loading and gait alternations may cause damage to the knee cartilage and the menesci. According to Grazio and Balen (2009), 69% of total knee arthroplasty (TKA) may be attributed to obesity.

Manek *et al.* (2003) stated that there are two major theories that could explain the association between obesity and KOA: biomechanical and systemic/metabolic mechanisms, where OA was also found in the hands of obese individuals. Furthermore, excess fat may have a direct metabolic effect on cartilage over and above the effects of stress, which acts indirectly to increase the risk of KOA. Sellam and Berenbaum (2013), on the other hand, stated that OA may have a systemic metabolic component and evidence from the literature supports the concept of metabolic OA. Furthermore, studies have demonstrated associations linking OA to several components of the metabolic syndrome, such as hypertension and diabetes or insulin resistance, independently from obesity or any of the other known risk factors for OA. Interestingly, it has been reported that, in women, the presence of obesity with at least two other metabolic syndrome components is associated with a higher risk of KOA compared to obesity alone.

According to Carman *et al.* (1994), obesity has been found to be a risk factor for non-weight-bearing joints, such as those in the hand. It has been reported that obese women with high BMI seem to have a higher risk factor for KOA than do non-obese women (Grazio and Balen 2009; Spector *et al.,* 1994). However, it has been concluded that BMI is a substantial and independent risk factor for KOA (Nicolella *et al.,* 2012).

Similar to obesity, BMI could have a biomechanical or metabolic effect on the knee joint (Wilson *et al.,* 2011).

### 2.2.4 Joint injury, deformity, and physical activity

Joint injuries, including anterior cruciate ligament (ACL), collateral ligament, and meniscal injuries as well as joint fracture and dislocation increase the risk of subsequent KOA (Englund *et al.,* 2009; Felson, 2013; Gelber *et al.,* 2000). In their systematic review and meta-analysis study, Blagojevic *et al.* (2010) reported that previous knee trauma is one of the main risk factors consistently associated with KOA, and, moreover, it increases the risk 3.86 times.

It has been hypothesised that OA is caused by increased forces across a local area of a joint, either from abnormal anatomy, excess overall load such as injury during sports or due to obesity, or a combination of anatomy and excess load. Injured meniscus and meniscectomies increase joint cartilage contact stress through altered load transmission, decreased shock absorption, and decreased joint stability. The greater the meniscus area removed, the worse the KOA progression is. ACL tears when accompanied with meniscal tears are more likely to lead to KOA (Englund *et al.,* 2009). However, Keays *et al.* (2010) reported that the incidence of KOA after ACL reconstruction is relatively high, reaching 50% six years after surgery. Meniscal tears and meniscectomies as a major risk factor provide evidence that abnormal mechanics cause OA (Felson 2013).

However, varus (bow-legged) and valgus (knock-kneed) malalignment of the knee joint is a substantial risk factor for progression of KOA. Varus alignment increases risk of subsequent medial KOA progression, whereas valgus alignment increases risk of subsequent lateral KOA progression (Sharma *et al.,* 2001). Sharma *et al.* (2010) found that varus malalignment increases the risk of the initial development of KOA.

Despite that physical activities, including physical activity during leisure and moderate exercise, have been linked with reductions in pain and improvements in cartilage health (Hanna *et al.,* 2005; Manninen *et al.,* 2001; Roos and Dahlberg 2005; Toivanen *et al.,* 2010), there is evidence that heavy physical activities are positively related to the incident risk of radiographic KOA (McAlindon *et al.,* 1999; Michaelsson *et al.,* 2011).

### 2.2.5 Occupation

Occupational activities requiring repetitive use can be associated with a higher prevalence of KOA. Occupations involving kneeling, squatting, or lifting heavy objects such farmer, jackhammer operator, construction worker, miner, housekeeper, and truck driver, may increase the risk for KOA (Felson, 2013; Manninen *et al.,* 2002; McWilliams *et al.,* 2011; Palmer, 2012; Rossignol *et al.,* 2003). Coggon *et al.,* (2000) found that subjects who reported frequent kneeling, squatting, and heavy lifting at work were at risk of developing KOA.

In their systematic review, Maetzel *et al.* (1997) studied the relationship of KOA and mechanical occupational exposure. They found that there is evidence of a strong positive relationship between work-related knee bending exposure and KOA in men, but, in women, this relationship was inconclusive. Andersen *et al.* (2012) reported that male floor-layers and bricklayers in addition to health care assistants of both genders had the highest risks of KOA.

### 2.2.6 Ethnicity and genetics

It has been reported that ethnicity has a role in developing OA based on variations among racial and ethnic groups. In their comparative study, Zhang *et al.* (2001) found that older Chinese women have a higher prevalence of KOA than did women in

Framingham, Massachusetts (USA). They stated that these differences could be attributed to genetic differences and heavy physical activity among the Chinese. They also found that the prevalence of KOA among Chinese men is roughly similar to that among white men. Interestingly, despite that men in China work at manual labouring jobs for many years and also spent significant amounts of time in a squatting position, which can create stress on the knees, severe radiographic OA was more prevalent among the subjects in the Framingham Study compared with those in Beijing. Possible explanation of this is that high body weight predisposes to more severe structural change and not physical activity alone. However, it has been found that older people in a rural farming region of northern China have a high prevalence of symptomatic and severe radiographic KOA compared with their ethnic peers living in urban region, Beijing (Kang *et al.,* 2009).

Felson *et al.* (2002) conducted a study to compare characteristics of OA in different racial groups. They found that Chinese subjects have a much more lateral KOA than do Caucasian subjects in the Framingham group despite the fact that those Chinese women and men from Beijing have a prevalence of medial KOA similar to that in Caucasian men and women of the same age from Framingham.

OA has been known to have a strong genetic predisposition. Numerous family and twin studies showed increased prevalence of OA among relatives (Spector and MacGregor, 2004; Spector *et al.,* 1996; Valdes and Spector, 2008). Spector *et al.* (1996) investigated the genetic influences on OA in twin women and they found a clear genetic impact of KOA in radiographs of hands.

According to Das and Faroogi (2008), the fact that OA is multifactorial in origin may explain why OA behaves differently worldwide. They attributed these differences to genetic makeup, lifestyles, and nutrition. Furthermore, by citing from previous studies,

they stated that polymorphisms of many genes have been associated with OA in some geo-ethnic populations, for example the cartilage oligomeric matrix protein gene polymorphisms have been found to be associated with OA in Caucasian but not in Japanese populations. There are additional factors which can increase the risk of developing KOA; for example, nutritional factors (McAlindon *et al.,* 1996), weather (Wilder *et al.,* 2003), and educational status (Verbrugge *et al.,* 1991).

## 2.3 Definition and diagnosis of KOA

Different definitions and tools have been used to define OA. However, the definitions can be categorised into clinical or radiological definitions or both (Blagojevic *et al.,* 2010). The clinical presentation of OA is based on symptoms (patient's self-report) alone or with radiographic changes. Clinical features accompanied with radiographic investigation could provide a crucial diagnosis of KOA (Bosomworth 2009). Nonetheless, diagnostic tools for evaluating KOA are various and include patient history, physical examinations, radiology, and laboratory findings.

Pain is the primary symptom of KOA (Schuelert *et al.,* 2011). At the onset of the disease, the pain is initiated on movement and alleviated at rest. Later, as the disease progresses, this pain may become more persistent, and it may restrict mobility and disturb sleep (Michael *et al.,* 2010; Sakalauskiene and Jauniskiene, 2010). KOA is a disease which is characterised by loss of hyaline articular cartilage, which contains no pain fibres (aneural) and no blood vessels (avascular). This implies that the pain might arise from the surrounding structures after being affected; this can be a sign of advanced KOA (Bosomworth 2009; Dieppe and Lohmander, 2005; Michael *et al.,* 2010; Sakalauskiene and Jauniskiene, 2010). Felson *et al.* (2001) found that bone marrow lesions on Magnetic Resonance Imaging (MRI) are strongly associated with the presence of pain in KOA.

Stiffness, especially during early morning, is a common complaint of KOA. Loss of function of the affected joint is also one of the important symptoms of KOA, which may be exaggerated by the pain. Pain has the ability to restrict mobility and the ability to undertake physical activities, which can hasten disease progression, exacerbate joint pain, and ultimately inhibit daily activities and then lead to disability (Castaneda *et al.,* 2012; Schuelert *et al.,* 2011).

Signs that may be found by clinical examination include ROM reduction, which may be caused by the presence of osteophyte formation, pain avoidance, and capsular thickening (Reid and McNair, 2010). Crepitus is also one of the important signs related to KOA, and it may be caused by irregularities in the joint surface. Additional signs that may be noted include bony enlargement, muscle weakness, joint instability, and tenderness (Sarzi-Puttiniet *et al.,* 2005; Zhang *et al.,* 2011).

For clinical definitions and outcomes, the severity of KOA is often assessed using different patient self-reporting and scoring systems, such as the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index and the visual analogue scale (VAS) (Lu *et al.,* 2010; Michaeal *et al.,* 2010). The progress of KOA can be defined radiographically according to four main radiographic features (Figure 2.1). The first feature is joint space narrowing, which begins at the point of maximal loading within the joint. The second feature is osteophyte formation, which may be formed in an attempt to self-repair. Subchondral sclerosis is the third feature, which may be caused by deposition of new bone in an attempt to self-repair. The last feature is subchondral cysts, which appear between thickened subchondral trabecular (Buckland-Wright 2004; Gupta *et al.,* 2005; Heidari, 2011; Jacobson *et al.,* 2008).

For a radiographic definition of KOA, the most commonly accepted grading system is the Kellgren and Lawrence (KL) grading scale, which was established more than 40

years ago and still stands. The KL grading system assigns one of five grades (grades 0–4, with 0 being normal and 4 severe OA) (Kellgren and Lawrence, 1957). Another definition used is minimal joint space, which is a measurement of the shortest or narrowest distance between the two bones of the joint; for example, the femur and the tibia for the knee joint (Jacobson *et al.,* 2008; Swagerty and Hellinger, 2001).

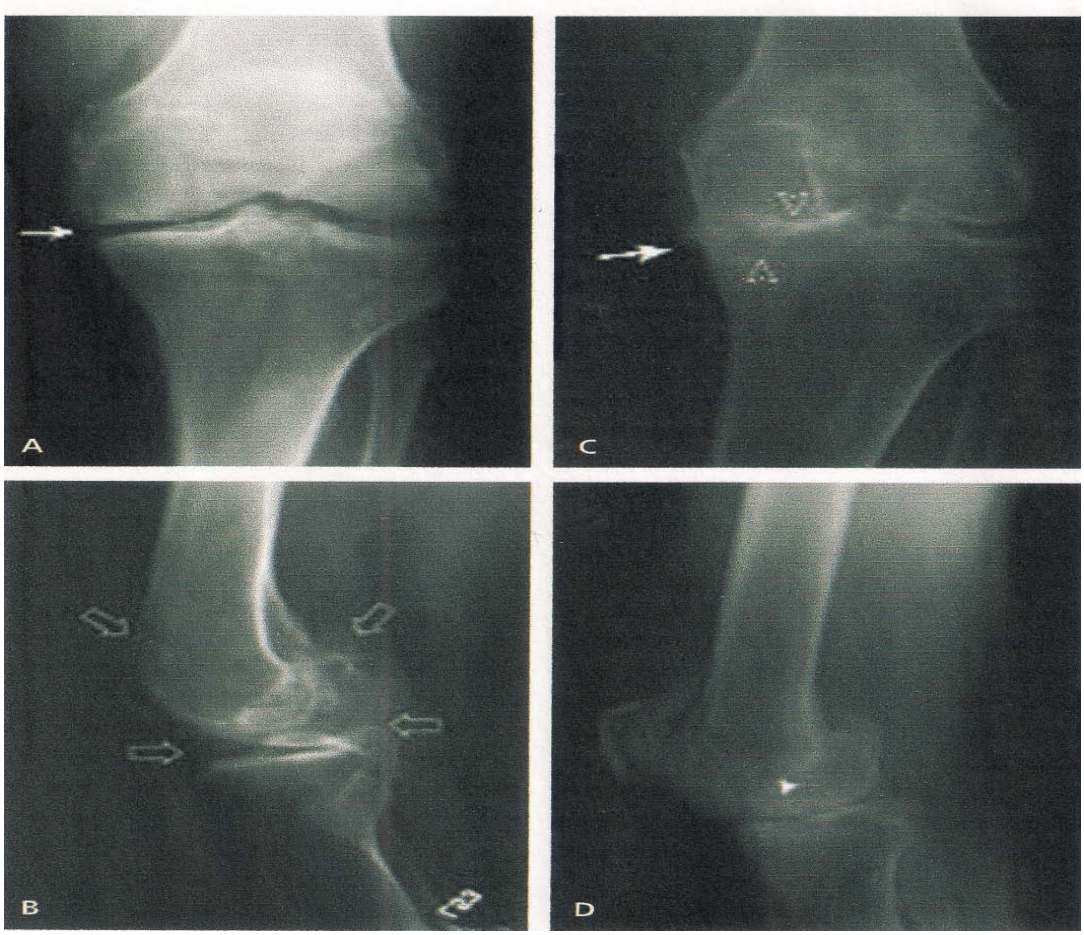


Figure 2-1 Main radiographic features of KOA. (A) Left knee shows medial joint space narrowing (arrow). (B) Left knee shows sclerosis with marked osteophyte formation (arrows). (C) Osteoarthritic changes with medial joint space narrowing (white arrow) (D) Subchondral cysts (solid arrowhead) (adapted from Swagerty and Hellinger, 2001)

Clinical symptoms, such as pain, stiffness, and loss of function, are not necessarily relevant to the level of joint pathological degeneration and vice versa (Bedson and Croft, 2008; Hannan *et al.,* 2000). However, it has been reported that a large proportion of those diagnosed with radiographic changes of OA are asymptomatic (Srikanth *et al.,* 2005). Altman *et al.* (1986) cited from a previous study, stated that 40% of those

diagnosed with degenerative OA based on radiographic assessment have no symptoms. Hannan *et al.* (2000) found in their study that only about 15% of patients with KOA and who were diagnosed via radiography complain of knee pain. They reported that there is a lack of correlation between the clinical definition and the radiographic definition. However, the preferred definition for KOA includes x-ray findings accompanied by symptoms such as joint pain to confirm diagnosis and exclude other possible conditions (Bosomworth, 2009).

Despite criticisms, plain radiographs have conventionally been used as the diagnostic tool to note, identify, and define KOA progression. It has been criticised for its unavailability in many parts of the world; which made the World Health Organization (WHO) (2003) recommend that a definition of OA based on a staging system based on symptoms or physical findings would be preferable. Another criticism is the difficulty in measuring changes over time. Furthermore, soft-tissue structures such as cartilage cannot be seen on x-ray. Radiographic technique, patient positioning, scoring features (bias), are all subject to criticism for using normal x-ray (Boulos *et al.,* 2003). However, where MRI technology is available it produces excellent images of the joint and its soft-tissue structures, and does not expose the patient to ionising radiation.

Ultrasonography is another way to demonstrate the soft tissues and fluid-filled spaces of joints. Previous technology is highly examiner-dependent and hence requires much experience for proper assessment (Michael *et al.,* 2010). Arthroscopy is one of the modalities that can be used to directly visualize cartilage and some of the soft-tissue structures for assessing the affected joint with OA. Another tool for evaluating OA is biomarkers. Biomarkers can be measured in serum, urine, or synovial fluid (Boulos *et al.,* 2003).

## 2.4 Treatment of KOA

The effects of OA, which today are already serious, are rapidly increasing to affect approximately 15% of the world's population; despite that, currently, there are no DMTs available for OA (Egloff *et al.,* 2012; Hellio Le Graverand-Gastineau, 2009; Schuelert *et al.,* 2011; Selvan *et al.,* 2012). Unfortunately, despite a wide variety of therapeutic options for the treatment of OA, including non-pharmacological, pharmacological, and surgical choices, currently there is no ability to stop the progress of the disease. Current treatment is for symptomatic relief, focusing on reducing symptoms, such as pain, which is the main reason for seeking health care; about 55% of patients with OA report pain as the worst feature of the disease.

The Osteoarthritis Research Society International (OARSI) recommendations emphasised that the treatment of KOA should be directed towards educating patients about OA, reducing joint pain and stiffness, maintaining and improving joint mobility, reducing physical disability and handicap, improving QoL, and minimising the progression of joint damage (Zhang *et al.,* 2008). Previous recommendations are similar to other guidelines for the treatment of KOA and hip OA, such as the American Academy of Orthopedic Surgeons (AAOS) and National Institute of Health and Clinical Excellence (NICE) (Zhang *et al.,* 2008). Figure 2.2 presents a sequential, pyramidal approach to the management of OA.

### 2.4.1 Non-pharmacological treatment

Non-pharmacological interventions such as education, physiotherapy, and occupational therapy are currently the first line of treatment and often are successful (Hunter and Felson 2006; Zhang *et al.,* 2007).

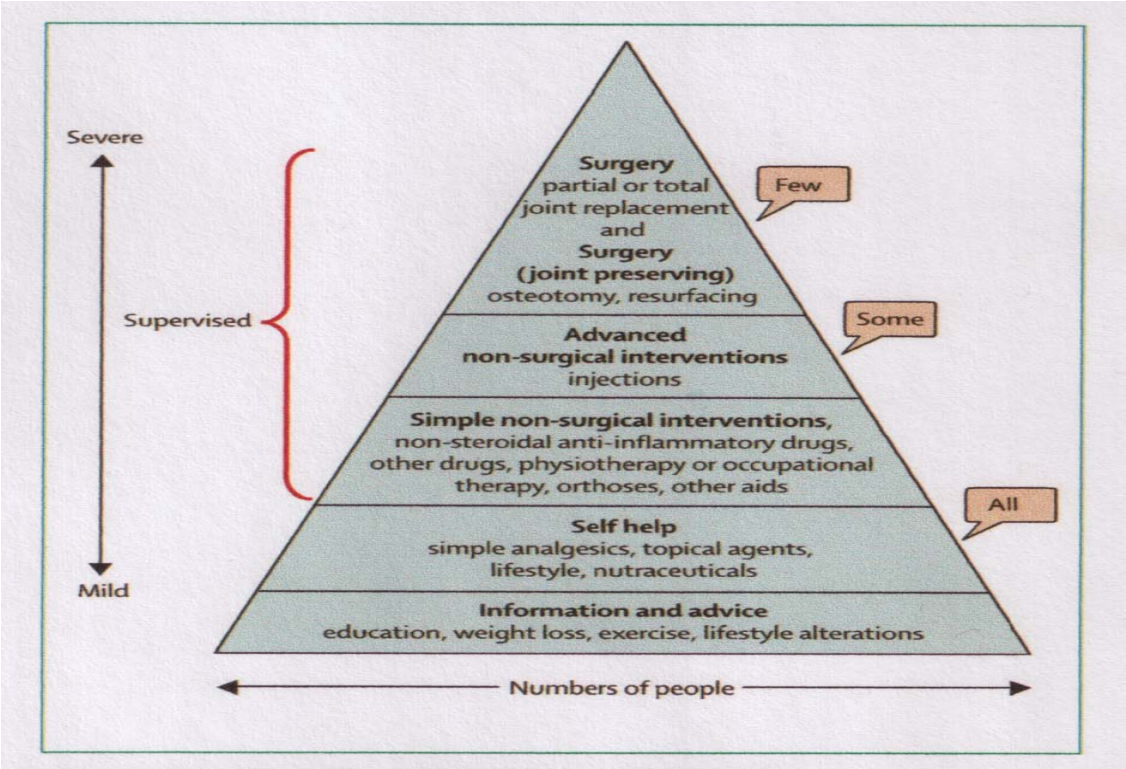


Figure 2-2 Principles of the management of OA (adapted from Dieppe and Lohmander, 2005)

#### 2.4.1.1 Prevention, education and behavioural modification

According to Michael *et al.* (2010), prevention is an important treatment for KOA. Joint protection plays a major role in preventing further damage of the joint structures. By eliminating the influences that can potentially affect or damage the joint components, development of OA can be prevented or at least slowed down. To achieve this goal, it is important for practitioners to educate their patients and make them aware of the extent of their condition and the importance of having an active role in its management.

Barlow *et al.* (2000) found that a self-management program for OA offers a number of important benefits, and it could be used as a useful adjunct to medical care. According to Pendleton *et al.* (2000), there is good evidence that education plays a role in reducing pain in patients with KOA. Furthermore, Hirano *et al.* (1994) reported that educational aspects can offer an additional 15–30% improvement over the effects of medication alone.

Patient education should include advice about weight reduction. Interestingly, a loss of 5 Kg may be associated with a 50% reduction in the possibility of developing symptomatic KOA as well as a reduction in the severity of joint pain (Grainger and Cicuttini, 2004; McGoey *et al.,* 1990). Furthermore, Christensen *et al.* (2007), in their meta-analysis, reported that a reduction of 5% of body weight within 20 weeks was related to symptomatic relief in patients with KOA. Moreover, it has been reported that for each 1 Kg of body weight lost, there is a 4 Kg reduction in the load on the knee joint per step (4800 Kg reduction for each Km walked) (Messier *et al.,* 2005).

Psycho-education, including patient education and self-management programmes, has a role in the management of patients with KOA (Jamtvedt *et al.,* 2008). Psychological support and coping strategies are very important for patients with chronic pain, such as KOA. Through the provision of information by explaining to patients the possible causes of their pain and that the symptoms they are experiencing are normal for their condition, their anxiety about their condition can be reduced (Adams *et al.,* 2006).

#### 2.4.1.2 Physiotherapy and occupational therapy

Pain and disability are the main reason for patients with KOA to seek health care, including physiotherapy (Peat *et al.,* 2001). Chronic pain patients, including patients with KOA, have a significant reduction in their physical activities as a result of their tendency to avoid pain, which leads, in turn, to a reduction and limitations in cardiovascular fitness, strength, endurance, coordination, and range of motion. These limitations can affect their ability to perform self-care and ultimately impair QoL (Strong 2002; Watson 2000).

Physiotherapy plays an essential role in managing KOA by helping to increase patient activity levels (Hawkeswood and Reebye, 2010). Exercise is a core recommendation in all international guidelines as a first-line management strategy for patients suffering

from KOA (Stemberger and Kerschan-Schindl, 2013). Patients with KOA have a significant decrease in knee muscle strength, especially the quadriceps muscle, the weakness of which is an early and common clinical feature of KOA. However, there is strong evidence that exercises can reduce pain and improve function in patients with OA (Alfredo *et al.,* 2011; Conroy *et al.,* 2012; Iwamoto *et al.,* 2011).

A wide range of different modalities are used by physiotherapists to control pain. For instance, TENS, which is a well-known pain-relieving modality, is used widely in physiotherapy clinics as a treatment to reduce chronic pain (Baxter and Barlas, 2002; Hawkeswood and Reebye, 2010). Other modalities are used for the same reason, but using a different form of energy, including shortwave, microwave, and shock-waves. Thermal heat or cold (e.g. hot pack, ice pack) and ultrasound are among the modalities used in physiotherapy clinics for controlling pain.

Acupuncture has been shown to be an effective treatment for KOA, which now could be applied by physiotherapists, either in the clinic as a member of a multidisciplinary team or patients could be referred from pain clinics for individual treatment (Hawkeswood and Reebye, 2010; Sweet, 1998). Within the field of electrotherapy, LLLT has been introduced by physiotherapists recently as a pain management therapy for localised and painful musculoskeletal conditions, including KOA (Abrisham *et al.,* 2011; de Carvalho *et al.,* 2012; Gur *et al.,* 2003a). Furthermore, it has been reported that LLLT stimulates reparative properties in human cartilage (Fukuda *et al.,* 2011). More details are presented in Section (3.8.2) on page 53.

Manual therapy, such as mobilization, manipulation, and soft-tissue massage that uses manual force is widely used in physiotherapy clinics. It can improve the mobility and extensibility of restricted joints and their connective tissues, resulting in decreases in the intra-articular pressure (Hoeksma *et al.,* 2005). It has been shown that manual therapy

reduces pain and improves function in KOA patients (Bialosky *et al.,* 2009; Pollard *et al.,* 2008). Furthermore, manual therapy can delay the need for TKA in patients with KOA (Deyle *et al.,* 2000; Zeni *et al.,* 2010).

Occupational therapy plays a major role in joint protection by providing patients with assistive devices, such as canes, braces and insoles, which have great benefit when used properly. Using these devices is recommended by the American College of Rheumatology (ACR) 2012. In addition, wedged insoles, can be used to realign the limb, which reduces the load on joints and ultimately reduces pain and improves function (Hochberg *et al.,* 2012; Recommendation for the medical management of osteoarthritis of the hip and knee 2000; Stemberger and Kerschan-Schindl, 2013).

## 2.4.2 Pharmacological treatment

In many cases of patients with KOA, non-pharmacological treatment is not adequate to control pain or improve functional status; even those who undergo surgery 6-30% still have persistent knee pain. Therefore, the logical next step is the use of pharmacological treatment (Cheng and Visco, 2012; Le Loet *et al.,* 2005; Zhang *et al.,* 2011).

### 2.4.2.1 Analgesics, NSAIDs

NSAIDs are the most widely prescribed medications for patients with KOA, although they are associated with serious side effects, including bleeding and gastric ulceration. Unfortunately, it has been reported that 20–30% of deaths from peptic ulcer disease in elderly people may be related to the use of NSAIDs (Griffin *et al.,* 1988). Therefore, treatment of KOA should be tailored to the individual patient, and many factors need to be taken into account prior to any treatment, such as age, co-morbidity, and the presence of inflammation. For mild to moderate pain without inflammation, paracetamol (acetaminophen) is commonly used as self-medication because of its relative safety. For

those unresponsive to paracetamol, particularly in the presence of persistent pain and inflammation, NSAIDs would appear to be the logical next step (Cheng and Visco, 2012; Pendleton *et al.,* 2000). Topical analgesics, such as capsaicin cream or topical NSAIDs could be used as monotherapy or adjunctive treatment (Sarzi-Puttini *et al.,* 2005).

#### 2.4.2.2 Intra-articular therapy

Intra-articular joint injection of glucocorticoids may be used for treating KOA, especially in the presence of effusion and local inflammation. Intra-articular injection of hyaluronan is currently available for the treatment of KOA. It is thought to help replace the synovial fluid and facilitate shock absorption and lubrication (Sarzi-Puttini *et al.,* 2005; Walker-Bone *et al.,* 2000).

### 2.4.3 Surgery

Initial treatment for patients with KOA should be conservative (pharmacological and non-pharmacological), but if it fails and symptoms persist, surgery could then be considered (Ronn *et al.,* 2011). There are many kinds of surgical procedures carried out, and the options depend on factors such as the patient's age, sex, the location, and stage of OA, level of activity, co-morbidities and weight (Ronn *et al.,* 2011). Arthroscopic lavage and debridement of the knee (e.g. shaving of rough cartilage or smoothing of the degenerated meniscus) is a successful option for younger and middle-aged patients with KOA accompanied by evident lesions of the meniscus or cartilage flaps (Felson *et al.,* 2000; Ronn *et al.,* 2011).

Osteotomies (realignment surgery) around the affected knee are another surgical option, performed for unicompartmental OA associated with varus or valgus deformity, especially in young and active patients with early OA. The efficacy of this surgery is to

realign osteoarthritic joints with the intent of relieving joint pain and improving function (Egloff *et al.,* 2012; Ronn *et al.,* 2011).

TKA, by all measures, is a well-accepted method for treatment of advanced KOA. Durability of prosthetic components is limited to about 15–20 years, therefore, whenever possible, use on patients younger than 60 years should be avoided. By TKA surgery, the pain and disability of end-stage OA can be eliminated, restoring patients to near normal function and improving their QoL. Despite its safety and efficacy, it suffers from several problems and complications, such as persisting pain, femoropatellar problems, loosening of components, infections, and stiffness of the knee (Felson *et al.,* 2000; Ronn *et al.,* 2011).

Arthrodesis, or joint fusion, successfully relieves pain and is commonly performed on the spine and in small joints, but not in the major proximal joints (Felson *et al.,* 2000). Indication for knee arthrodesis in patients with KOA is severe pain and instability of the knee joint following an infection at a previous TKA. Patients with this surgery will have some functional difficulties with climbing stairs and with sitting, in addition to some complications such as an arthrodesis of the contralateral hip or knee, significant OA in the ipsilateral hip or ankle, or shortening of the leg (Zhang *et al.,* 2008).

## 2.5 Search strategy

Search strategy used for the current study to identify studies and relative information from electronic databases is presented in Appendix I.

# Chapter 3 Review of the literature of low level laser therapy (LLLT)

## 3.1 History and Background of Laser

LASER is an acronym for Light Amplification by Stimulated Emission of Radiation. The applications of lasers are associated with many fields, which range from the use of very high-power lasers in military and medical applications to the very low power laser used in supermarket barcode systems, lecture pointers, and compact discs (Baxter, 1994).

Interestingly, the sun was the first source of medicinal light, which was classically referred to as heliotherapy (Bloch, 1990). Heliotherapy has been practiced for thousands of years and was employed in the treatment of several conditions, including epilepsy, asthma, scurvy, rickets, rheumatoid arthritis, and depression (Rosenshein, 1997).

At the turn of the 20th century, an artificial source of therapeutic ultraviolet (UV) was developed by Dr Niels Finsen, who won the Nobel Prize for medicine in 1903 for his work with UV in the treatment of dermal tuberculosis. In the 1950s, Schawlow and Townes amplified a beam of microwaves producing Microwave Amplification by Stimulated Emission of Radiation (MASER), putting into practice what had been conceived earlier by Albert Einstein, who in 1917, showed that the existence of equilibrium between electromagnetic radiation and its interactions with matter required a previously undiscovered radiation process called stimulated emission. Later, in 1960, Theodore Maiman amplified light using a ruby crystal as a lasing medium emitted light in the red part of the visible spectrum at a wavelength of 694.3 nm. As a result, the birth of laser was declared (Baxter 1994; Jackson *et al.,* 2001).

In 1961, Javan and his colleagues developed the first gas laser using a mixture of two gases, helium (He) and neon (Ne), which emitted red and infrared light. In the same year, Johnson developed a laser emitting in the invisible infrared spectrum using an

yttrium aluminium garnet (YAG) doped neodymium (Nd: YAG) laser. Not long afterwards, in 1962, the argon laser (a gas laser giving a blue-green visible beam) was discovered by Bennett and his associates (1962). Two years later, in 1964, Patel developed the carbon dioxide ($CO_2$) laser, which emits in the invisible infrared portion of the spectrum (Jackson *et al.,* 2001; Peng *et al.,* 2008).

In 1967, a few years after the first laser was created, Professor Endre Mester conducted a study to investigate if laser radiation might cause cancer in mice. He shaved the hair of their backs and divided them into two groups, and then he irradiated the shaved area of one group with a low-powered ruby laser (694nm). The irradiated mice did not get cancer; instead, he noted that the hair grew back quicker at the irradiated area than it did in the untreated group. This was how 'laser bio-stimulation' was discovered (Baxter and Barlas 2002; Huang *et al.,* 2009).

Clinical laser use is based upon the photo-thermal and photo-ablative interactions with tissue at relatively high-power and energy densities (Peng *et al.,* 2008). In surgery, lasers are used to cut (as alternatives to metal scalpels), weld, and even destroy tissue, such as in tumour ablation and tattoo removal. Ophthalmic surgeons were the first to use the pulsed ruby laser for the treatment of detached retina in humans (Baxter and Barlas, 2002).

## 3.2 Laser physics

### 3.2.1 Principal components of a laser device

The laser device, in order to produce laser radiation, must consist of three basic components, namely a lasing medium, a power source, and resonating cavity (Figure 3.1).

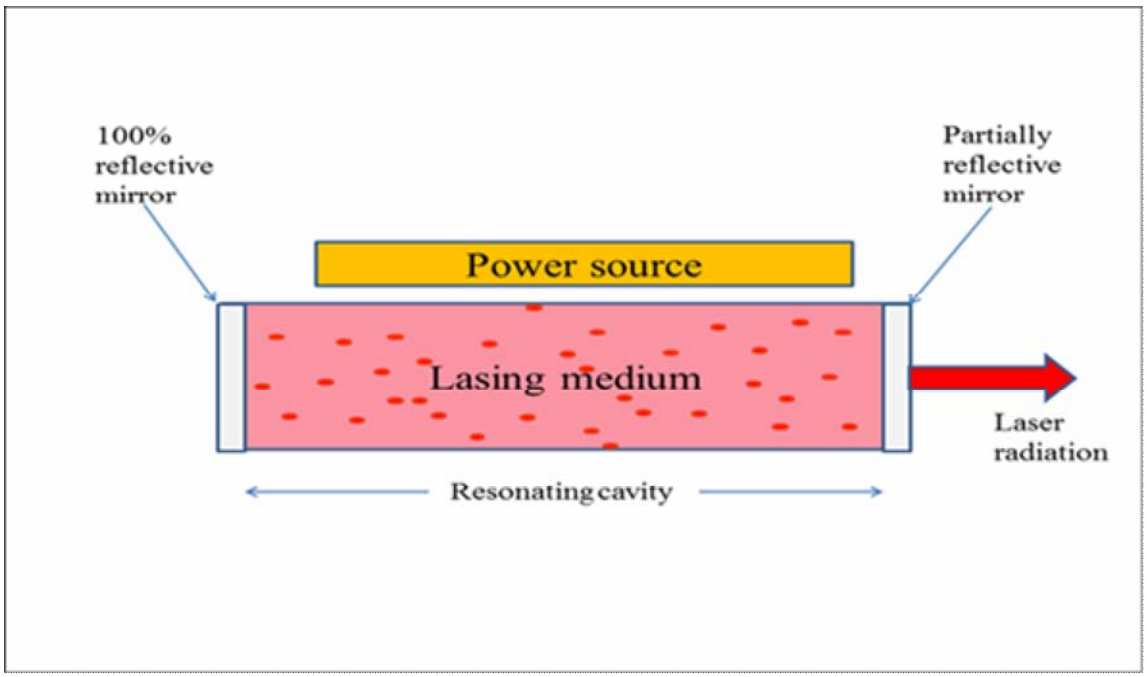


Figure 3-1 Principal components of a laser device

#### 3.2.1.1 Lasing medium

A laser medium can be gaseous, liquid, solid, crystal or semiconductor. These media should have the property of absorbing energy generated by an external power source and ultimately giving off energy as photons of light. A photon (quantum) is a particle of energy that travels at a speed of $3\times10^{8}$ ms; where the brightness of light is the number of photons and the colour of the light is the energy contained in each photon (Rojas and Gonzalez-Lima, 2011).

#### 3.2.1.2 The power source

The power source might be electrical, chemical, or optical energy, and it is used to excite or 'pump' the laser medium to higher energy level laser radiations (photons).

#### 3.2.1.3 Resonating cavity

The resonating cavity consists of the lasing medium within a central chamber, which is located between two parallel mirrors at either end. The two mirrors are positioned at right angles to the longitudinal axis of the medium and also placed a fixed distance apart, allowing excited atoms of the laser medium (photons) to move back and forwards across the chamber. The rear mirror is 100% reflective, and the front one allows a small percentage of the laser beam to be transmitted as the output signal (output coupler) (Baxter, 1994).

The vast majority of the atoms of the lasing medium are at the lowest energy level prior to the activation of the power source in the medium. This phase is termed the ground state. When the energy source is supplied from the power source and is directed into the resonating cavity, the energy is absorbed by the electrons of the medium which are then excited, and they store an exact quantum of energy. At this stage, the atoms in the excited state are unstable, and their electrons spontaneously return to their ground level, releasing their temporarily stored extra energy as a photon of light. Radiated photons have a wavelength specific to the atoms of the lasing medium. This process is called spontaneous emission of radiation (Figure 3.2 a).

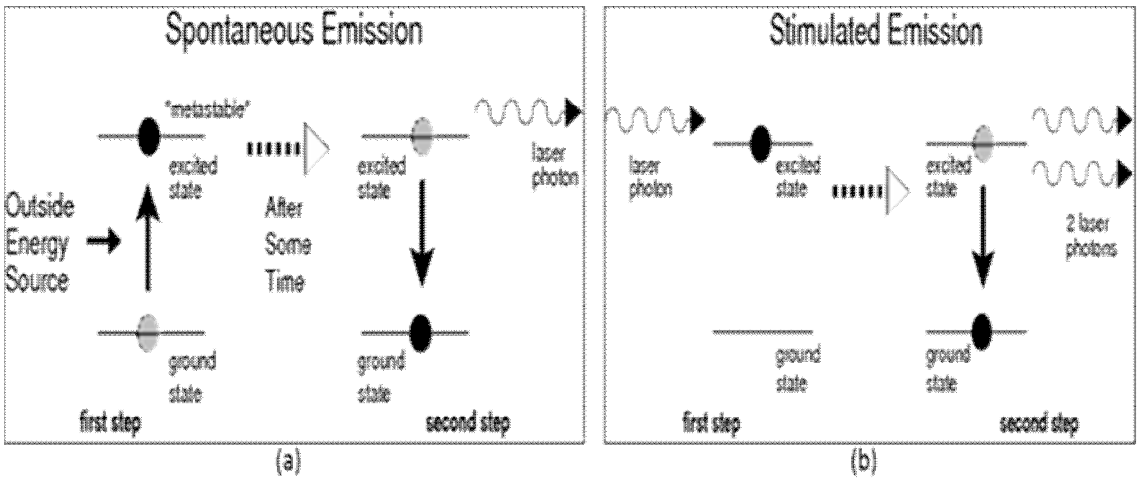


Figure 3-2 Spontaneous and stimulated emission of radiation (adapted from http://cnx.org/content/m39557/1.1/)

The releasing photon must have the same characteristics as the energy and wavelength that will be released when the electron returns to the ground phase. This process is referred to as stimulated emission of radiation (Figure 3.2 b). Ultimately, the intensity of the intra-cavity energy is amplified using the two parallel mirrors, permitting a portion of the energy to leak out through the partially transmissive front mirror (Baxter 1994; Tuner and Hode, 2002).

## 3.2.2 Characteristics of laser radiation

Laser radiation has important characteristics over the ordinary light source (Figure 3.3).

### 3.2.2.1 Monochromatic

Laser light is of a single and defined wavelength, which gives a single pure colour, such as the He-Ne laser that produces a red laser beam. A laser light is, consequently, said to be highly monochromatic (single coloured). In contrast, ordinary light consists of all colours of the spectrum (polychromatic) (Baxter, 1994; Tuner and Hode, 2002) (Figure 3.3).

#### 3.2.2.2 Coherent

All energy waves of the laser light travel in phase (synchronicity), and the light emitted from ordinary light is described as incoherent. Laser light has the ability to stay in phase for very long distances, with a relatively little beam spread (Baxter, 1994) (Figure 3.3).

#### 3.2.2.3 Collimation

This refers to the minimal divergence of the laser beam, and there is little intensity loss as distance increases. This allows a concentrated beam to be focused on a relatively small area. The He-Ne laser is the most highly collimated low-power laser used in therapeutic applications (Baxter 1994) (Figure 3.3).

Previous characteristics might play an important role in the clinical application of a laser. It has been reported that the mechanism of LLLT at the cellular level has been attributed to the absorption of monochromatic visible and near infrared (NIR) radiation by components of the cellular respiratory chain (Huang *et al.,* 2009). Furthermore, it has been found that coherent light has a positive effect on an injured nerve; whereas non-coherent light has been known to affect the injured nerve adversely (Smith, 2010).

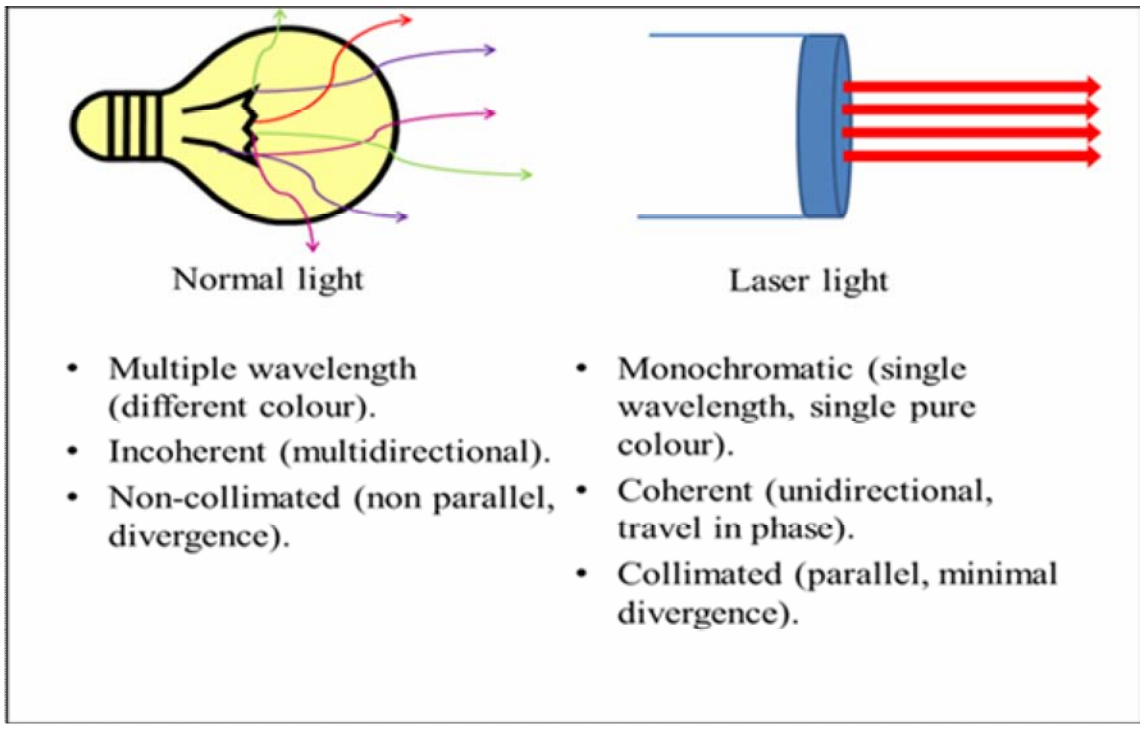


Figure 3-3 Characteristics of laser radiation versus ordinary light

## 3.3 Laser types

Laser type is wavelength dependant, as well as the lasing medium (Figure 3.4). A variety of therapeutic laser systems are currently available for clinical applications, including gas laser medium, dye (liquid) lasers, and semiconductor lasers. Gas lasers, such as the carbon dioxide, argon, and Nd: YAG are commonly used in the surgical field, with subsequent ability to vaporize and coagulate tissue (de Paula Eduardo *et al.,* 2010; Peng *et al.,* 2008).

Dye lasers, which are usually liquid solutions, can be turned to a much wider range of wavelengths by changing the chemical composition of the lasing medium. In medicine, these lasers are applied in several areas, including blood vessel disorders, kidney stones, and dermatology, such as in scars and for tattoo removal (Peng *et al.,* 2008; Shankarling and Jarag, 2010).

According to da Silva *et al.* (2010), the most frequently used types of lasers in the field of LLLT are helium-neon (He-Ne) lasers and diode lasers. Diode lasers (semiconductor

lasers) include gallium-aluminium-arsenium (GaAlAs), arsenium-gallium (AsGa), and indium-gallium-aluminium-phosphide (InGaAlP) lasers. Unlike lasers used in surgery, the effects of LLLT are photochemical rather than thermal (Tuner and Hode 2002).

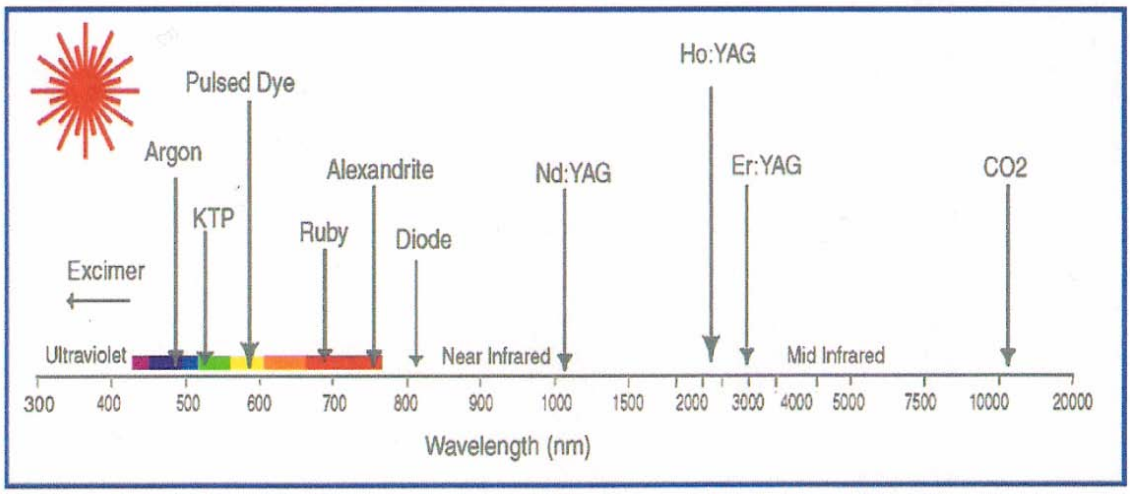


Figure 3-4 Wavelength of common medical lasers (adapted from Peng *et al.,* 2008)

Laser light can also be described according to its beam as continuous-wave (CW), pulsed, or quality switched (Q-switched). CW lasers consist of a consistent beam of relatively low steady output power. The beam of the pulsed lasers is emitted in bursts, output power with peak powers higher than CW lasers. This operation is controlled by mechanical shutters or electrical switches; however, the pulsed light can be set typically in millisecond (ms) with regards to surgical lasers, and it is measured by the number of pulses per second or Hertz (Hz) (Acland and Barlow, 2000). Quality switching is a technique used to produce a pulsed output beam with extremely high peak power (Wohlmuth *et al.,* 2009). It has been reported that Q-switched lasers are used clinically to remove tattoos (Kilmer and Anderson 1993).

## 3.4 Laser parameters

The laser system could be described through its parameters, which include the laser wavelength, power output, power density (intensity), and energy density (fluence, or

dose). It has been reported that parameters such as wavelength and fluence play a major role in cellular metabolism during therapeutic application. Furthermore, LLLT at certain wavelengths and fluencies can stimulate cell proliferation (AlGhamdi *et al.,* 2011; Yu *et al.,* 1997). Huang *et al.* (2009) indicated that LLLT can be likened to other forms of medication, and that LLLT has its active ingredients or 'medicine' (irradiation parameters) and a 'dose' (the irradiation time). Table 3.1 shows major parameters of LLLT.

### 3.4.1 Wavelength

Light is a type of electromagnetic radiation and a form of energy called luminous energy. Electromagnetic waves have crests and troughs. The wavelength is the distance between successive crests or troughs of the same phase measured in nanometres (nm). The number of oscillations per second is called frequency; whereas the difference between crests and troughs is called amplitude (Rojas and Gonzalez-Lima, 2011). Each laser has distinct uses depending on the wavelength and power output; moreover, penetration of the laser beam into the target tissue is wavelength dependent (Figure 3.5). Furthermore, laser with wavelengths ranging from 600 to 700 mm is used for treating superficial tissues, whereas wavelengths between 780 and 950 nm are used for deeper tissues (Chung *et al.,* 2012; Hamblin and Demidova, 2006).

### 3.4.2 Power output

A laser's power output (radiant power) is the amount of energy it produces, and it is measured in Watts (W). However, because the laser radiation in therapeutic application, especially in LLLT is below 1W, it is expressed in milliwatts (mW) (Baxter, 1994). The

stronger the laser radiant power (mW) is the shorter the required treatment time is (Hawkins and Abrahamse, 2007).

### 3.4.3 Power density

Power density (irradiance) or the light intensity of the beam on the area of irradiation is expressed in mW per square centimetre, $mW/cm^2$, which is defined by the power output divided by the area of the target tissue being irradiated by the laser light, with the area being defined by the beam spot size ($r^2$) at the tissue surface (Baxter, 1994). Then, power density measures the amount of power per unit area leaving the laser probe. The larger the area irradiated the greater the reduction in power density.

### 3.4.4 Energy density

Energy density (fluence, or dose) measures the amount of energy received by a given target tissue. It is expressed in joules per square centimetre ($J/cm^2$) as a product of power (mW) and time (s) per spot size ($cm^2$). The fluence (dose) of the laser required depends upon the laser wavelength, type of tissue, condition and depth of the target tissue, chronic or acute problem, pigmentation, and treatment technique (contact versus non-contact), whereas the laser fluence administration is influenced by the power (mW), irradiance ($mW/cm^2$), time (s), and treatment intervals (Hawkins and Abrahams, 2007). Furthermore, it has been stated that there is evidence suggesting that energy density as well as power density are key biological parameters for the effectiveness of laser therapy (Sommer *et al.,* 2001).

**Table 3-1 Major parameters of LLLT (adapted and modified from Rojas and Gonzalez-Lima 2011)**

| Parameter | Unit | Explanation |
|---|---|---|
| Wavelength | nm | Wavelength is the distance between wave peaks. Light is a form of energy with wave behaviour. Photo-acceptors exhibit different sensitivities to different wavelengths. The most effective LLLT wavelength range is 600–1100 nm. Light visible to the human eye is 400–700 nm. The higher the wavelength, the lower the energy. |
| Energy | J | Energy (E) is the frequency (v) of radiation by Planck's constant (h) of $6.626 \times 10^{-34}$ Js (E = hv). Energy of a photon depends on the frequency of radiation (Ephoton = hv). A photon is a particle of electromagnetic radiation with zero mass and a quantum of energy (minimum E gained or lost by atom). Energy (J) = Power (W) × Time (s). |
| Power | W | Amount of energy (J) transferred or flowing per unit of time (W = J/s). |
| Irradiance | $W/cm^2$ | Power (W) per surface area ($cm^2$). Also called power density or light "intensity". Irradiance = Power (W) / Area ($cm^2$). |
| Radiant exposure | $J/cm^2$ | Energy (J) per surface area ($cm^2$). Equivalent to power density per unit of time (s). Also called fluence, energy density, or light "dose." Thus, "dose" can be easily varied by changes in exposure time. However, at the same energy density ($J/cm^2$) variations in either irradiance ($W/cm^2$) or time may cause different LLLT effects on tissues. |
| Exposure time | s | Time during which the target tissue is exposed to light. |
| Wave type | Continuous versus pulsed | Continuous waves may be advantageous for transcranial applications. Pulse waves may decrease thermal effects. Pulse Average Power = Peak Power (w) × Pulse width (s) × Pulse Frequency (Hz). |

## 3.5 Laser classification and hazard

The laser produces an intense beam of light which could be directed, reflected, or focussed upon an object. Laser light will be partially absorbed, raising the temperature of the surface, causing an alteration or deformation of the material. Under certain circumstances (laser power, wavelength, and exposure duration) exposure to laser light can result in tissue damage to the eye and skin.

According to the American National Standards Institute (ANSI) as specified in the ANSI Standards Z136.1-2007, ‘‘The Safe Use of Lasers’’, the laser light is classified into 7 classes (1, 1M, 2, 2M, 3R, 3B and 4) to indicate the level of laser beam hazard and maximum Accessible Emission Levels (AELs), which is the maximum accessible level of laser radiation permitted within a particular laser class.

A *class1 laser system* produces laser that is considered being safe during operation and is exempted from any control measures or other forms of surveillance. The *class 1M laser system* produces laser that is considered being safe during normal operation unless the beam is viewed with an optical instrument such as an eye-loupe (diverging beam) or a telescope (collimated beam). It is also exempt from any control measures or other forms of surveillance during normal operation. A *class 2 laser system* produces laser light that only emits visible radiation in the wavelength range from 400 nm to 700 nm with output less than the appropriate AEL. It is considered to be safe for accidental viewing as eye protection is afforded by aversion responses. A *class 2M laser system* is the same as class 2, however, total output is in excess of that normally permitted for class 2 and potentially hazardous if viewed with certain optical aids.

A *class 3R laser system* produces laser light that is in the wavelength range from 302.5 nm to 1mm where the AEL can be exceeded, but with a low risk of injury. The class 3R

laser is normally not a diffuse reflection or fire hazard. A *class 3B laser system* produces laser that is hazardous if the eye is exposed directly. Protective eyewear is required for direct viewing of the class 3B laser and laser units must be equipped with a key switch and a safety interlock. The laser unit used in the current study falls in this range. A *class 4 laser system* produces high-power lasers that exceed the AELs of other classes and are capable of producing hazardous diffuse reflections and causes skin and eye injuries. Its use requires extreme caution (American National Standard for Safe Use of Laser; ANSI Z136.1, 2007). Table 3.2 shows 4 major hazard classes (I to IV) of lasers recognised by the FDA.

**Table 3-2 major hazard classes (I to IV) of lasers recognised by the FDA (adapted from:http://www.fda.gov/radiationemitting productss/radiationemittingproductsandprocedures/homebusinessandentertainment/laserproductsandinstruments/default.htm)**

| Class, FDA | Class IEC | Laser Product Hazard | Product Examples |
|---|---|---|---|
| I | 1, 1M | Considered non-hazardous. Hazard increases if viewed with optical aids, including magnifiers, binoculars, or telescopes. | -Laser print<br>-CD player<br>-DVD players |
| IIa, II | 2,2M | Hazard increases when viewed directly for long periods of time. Hazard increases if viewed with optical aids. | -Bar code scanners |
| IIIa | 3R | Depending on power and beam area, can be momentarily hazardous when directly viewed or when staring directly at the beam with an unaided eye. Risk of injury increases when viewed with optical aids. | -Laser pointers |
| IIIb | 3B | Immediate skin hazard from direct beam and immediate eye hazard when viewed directly. | -Laser light show projectors<br>-Industrial lasers<br>-Research lasers |
| IV | 4 | Immediate skin hazard and eye hazard from exposure to either the direct or reflected beam; may also present a fire hazard. | -Laser light show projectors<br>-Industrial lasers<br>-Research lasers<br>-Lasers used to perform LASIK eye surgery |
| IEC, International Electro-technical Commission | | | |

## 3.6 Laser penetration

Penetration depth of the laser beam is a wavelength dependent (Litscher and Opitz, 2012; Rojas and Gonzalez-Lima, 2011) (Figure 3.5). Laser light with a longer wavelength penetrates deeper, whereas, laser light with a shorter wavelength penetrates superficially. Furthermore, it has been stated that the penetration depth of laser light depends on the type of tissue being irradiated and the frequency of laser light (Ezzati *et al.,* 2009; Rojas and Gonzalez-Lima, 2011). Blue-green light yields poor penetration as it is absorbed in biologic pigments, whereas, red and NIR wavelengths (700 to 1200 nm) penetrate considerably deeper (Houreld, 2006). Laser beam continues to penetrate deeper until water absorption becomes relatively high, causing the penetration depth to decrease rapidly (Welch *et al.,* 1989). A $CO_2$ laser beam is completely absorbed in water, making the penetration rate in the tissue to be weak. Nd: YAG laser beam is absorbed by protein, making its penetration quite high. He-Ne laser beam (red light) is absorbed less by blood, so its penetration rate is relatively high. A Laser beam from the diode laser, particularly the GaAlAs (830nm) has the highest penetration rate (Houreld, 2006). The GaAlAs (830nm) is identical to the one used in the current study.

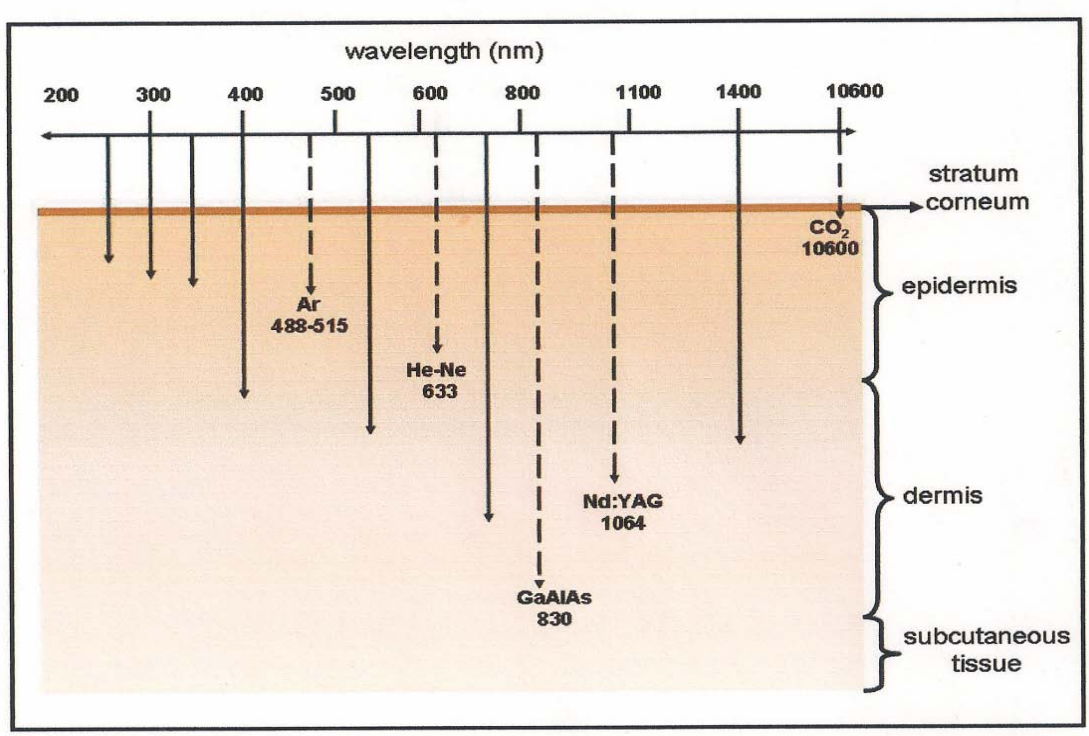


Figure 3-5 Penetration depth of some common medical lasers in human skin tissue (adapted from Houreld, 2006)

## 3.7 Medical laser

Despite that laser is used today by a large variety of professions (see Section 3.1), its use in medicine is one of the most meaningful applications of laser technology. The clinical use of laser therapy is based upon the photo-thermal and photo-ablative interactions of laser with tissue at relatively high-power and energy densities (Peng *et al.,* 2008).

Lasers are used in most medical disciplines as a surgical tool, as well as diagnostically, and as a therapeutic modality. The laser can cauterize deeply (alternatives to metal scalpels) as it cuts, and reducing the surgical trauma caused by a scalpel. It can vaporize the surface of a tissue as in tattoo removal. Also, it can weld and even destroy tissues such as in tumour ablation. Ophthalmic surgeons were the first who administrated the laser in surgery using the pulsed ruby laser for the treatment of detached retina in humans (Baxter and Barlas, 2002; Peng *et al.,* 2008). Furthermore, light energy (optical

biopsy or optical diagnostics) is used to obtain information on the structure and function of tissue without disrupting it, as in early diagnosis of lung cancer (Peng *et al.,* 2008).

When the laser beam is directed towards tissue, it may be reflected, transmitted, scattered and/or absorbed and the optical properties of substances are characterised by coefficients for each of these events (Chung *et al.,* 2012). Only about 3% of the directed light beam is reflected while the remaining light goes into the tissue where absorption and scattering take place.

Both the absorption and scattering of light in tissue are wavelength dependent. The laser photons that enter tissue are scattered once or multiple times until they either escape or are absorbed. A scattering of laser photons occurs after it has entered the tissue spreading out within the tissue resulting in irradiation of the surrounding area. Depending on the rate of laser photons absorbed within the tissue; the energy (heat oscillations) is delivered. As a result, depending on the degree of generating energy, target tissue may be carbonized, vaporized or coagulated, or the tissue proteins may be degraded or denatured (Houreld 2006; Peng *et al.,* 2008). The absorption and scattering of light in tissue form the basis of techniques using laser in medicine. The current study mainly focuses on the LLLT used in physiotherapy and rehabilitation, and it is beyond the scope of this research to discuss the laser technique used in surgery.

## 3.8 Low-level laser therapy (LLLT)

Shortly after Endre Mester, in 1967, discovered the ability of the He-Ne laser to increase hair growth and stimulate wound healing in mice, he began to use lasers on humans to treat patients with non-healing skin ulcers. Since then, LLLT has gained attention for treating a variety of medical conditions that require tissue repair, pain relief, inflammation reduction, preventing cell death and tissue damage. LLLT was

mainly employed as a treatment for wound healing and pain relief of musculoskeletal and soft-tissue injuries. In recent years, it has been broadened to treat serious diseases such as stroke, myocardial infarction, spinal cord injury, degenerative or traumatic brain disorders, and retinal disease (Chung *et al.,* 2012; Hashmi *et al.,* 2010; Rojas and Gonzalez-Lima, 2011).

According to Rojas and Gonzalez-Lima (2011), LLLT can be defined as the use of low power and high-fluence monochromatic or quasi-monochromatic light from lasers or light-emitting diodes (LEDs) in the red to NIR wavelengths (600–1100 nm) to modulate a biological function or induce a therapeutic effect in a non-destructive and non-thermal manner.

This treatment modality is termed LLLT because the optimum levels of energy density delivered are low compared with the high-power laser as practiced for ablation, cutting, and thermally coagulating tissue (Chung *et al.,* 2012). The effects of LLLT are photochemical rather than thermal such as the one used in surgery (Tuner and Hode, 2002). Furthermore, it can be referred to as photobiology or bio-stimulation. LLLT is variously known as low-power lasers, low-intensity laser irradiation, low energy laser therapy, cold laser therapy, photon therapy, phototherapy, photobiomodulation. Red and NIR lasers, usually in the range of 1mW to 500mW, are widely used in the field of LLLT and includes He-Ne lasers with a wavelength of 633nm and semiconductor lasers emitting light in the range of 780 to 950nm such as GaAlAs laser (Huang *et al.,* 2009; Kreisler *et al.,* 2003). It has been reported that lasers with wavelengths ranging from 600 to 700 nm are used for treating superficial tissues, while wavelengths between 780 and 950 nm are used for deeper tissues (Chung *et al.,* 2012; Hamblin and Demidova, 2006). Bjordal *et al.* (2003) reported that when the laser light hit the skin, its energy loss due to the skin barrier for continuous He-Ne (632nm) laser is 90%, for continuous

GaAlAs (820 nm) is 80%, and finally for GaAs (904 nm) infrared pulse laser the loss is 50%.

LLLT has become an increasingly mainstream modality and is practiced as a part of physiotherapy, physical medicine and rehabilitation (Baratto *et al.,* 2011; Chung *et al.,* 2012; de Carvalho *et al.,* 2012; Gur *et al.,* 2003a; Hashmi *et al.,* 2010; Vladimirov *et al.,* 2004). Moreover, it is used in a wide range of clinical settings ranging from dentistry, to dermatology and rheumatology (Chung *et al.,* 2012; Vladimirov *et al.,* 2003). According to Alfredo *et al.* (2011) the European League against Rheumatism (EULAR) suggests that LLLT should be considered when planning optimal treatment for OA.

Guidelines by the USA FDA stated that laser devices used for treating human and animals must meet Mandatory Performance Standards, which include ‘‘safety features and labelling to provide adequate safety to users and patients’. Therefore, FDA clearance for using laser devices means that it has ‘‘passed a quality assurance test and that it complies with the performance standard”. Although the use of LLLT is not new and has been practiced in clinical settings since the 1960s, the first cleared by US FDA was as late as 2002. The FDA granted 510 (k) approval for several companies to market lasers that provide LLLT. A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective. For example, in 2002, the FDA cleared the MicroLight 830-NM diode laser for treatment of carpal tunnel syndrome (FDA laser information, 2009).

### 3.8.1 Mechanism of LLLT

The light applied in laser therapy is usually red or NIR in the range of 600nm to 1000nm, known as the ‘optical window’, where the effective tissue penetration of light

is maximised, with a power density of between 1mW-5W/cm$^2$. In spite of its increasing use and application since discovery, LLLT as a therapeutic tool has been dogged by controversies because of its yet-to-be-understood biochemical mechanisms, making its application essentially empirical; also because of its lack of flexibility in terms of usage, since the following factors have to be chosen for each treatment: wavelength, fluence, power density, pulse structure, and timing of the applied light, a failure of which might affect the efficacy of treatment and possibly produce a negative therapeutic outcome (Chung *et al.,* 2012; Huang *et al.,* 2009).

The exact biochemical mechanisms of the action responsible for the therapeutic effects of LLLT are poorly understood in spite of its increasing use. However, there have been several attempts to provide an explanation, with many of these proposals suggesting that the underlying mechanism of action of LLLT could be at the molecular, cellular, and tissue levels. There is consensus, as to the following modes of action, that LLLT stimulates the mitochondria to increase adenosine triphosphate (ATP) production and regulates the reactive oxygen species (ROS) and the induction of transcription factors (Chung *et al.,* 2012; Hashmi *et al.,* 2010; Huang *et al.,* 2009).

#### 3.8.1.1 Cytochrome c oxidase and nitric oxide release

The first explanation for LLLT is that it follows the first law of photobiology, which states that for low-power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular photo-acceptors (Figure 3.6). Cytochrome c oxidase (Cox) is believed to be the principal photo-acceptor for the red-NIR range in mammalian cells. It has also been proposed that the mechanism for LLLT could possibly be by the photo-dissociation of nitric oxide (NO) from Cox, thereby enabling cellular respiration which would have been switched off by the excessive binding of NO to Cox inside the mitochondria. The association between NO and Cox is able to inhibit respiration in cells by totally

dislodging oxygen, particularly in stressed or hypoxic cells. LLLT reverses this association by the inhibiting oxygen dislodgment and thus stimulates unimpeded cellular respiration and increases cellular ATP thereby enhancing cellular energy levels and up-regulating the cyclic AMP molecule needed for several signalling pathways (Chung *et al.,* 2012; Hawkins and Abrahamse, 2007; Huang *et al.,* 2009).

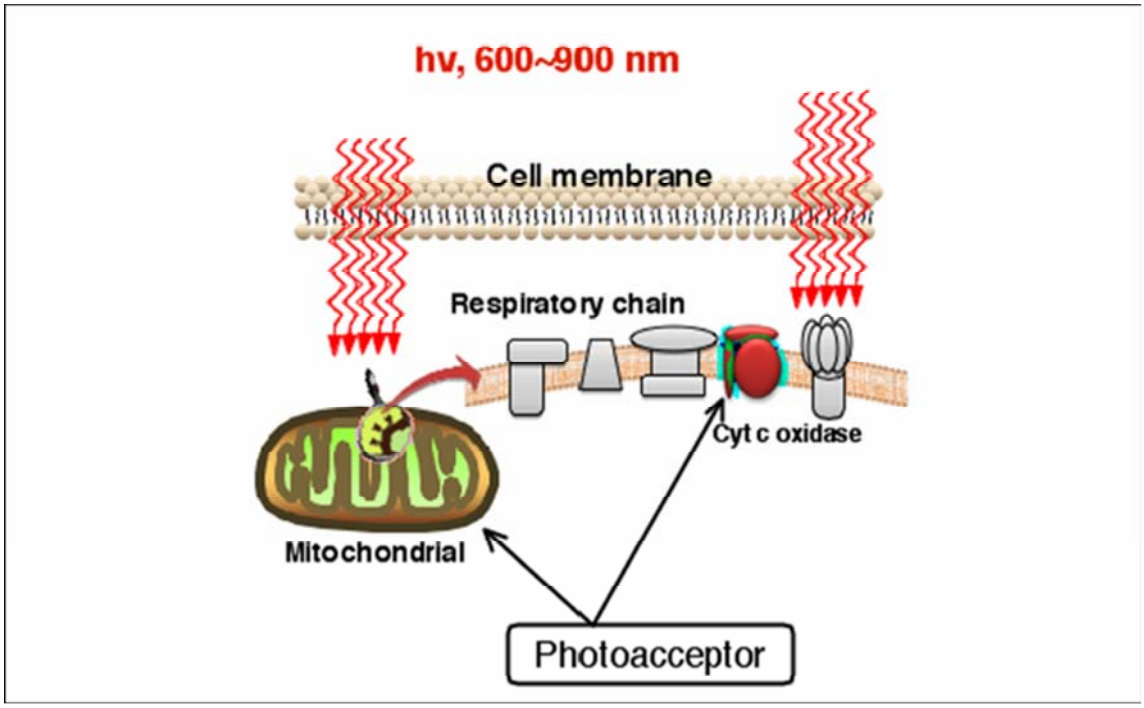


Figure 3-6 Diagrammatic illustration of the absorption of red and near infrared light (NIR) by specific cellular photo-acceptor inside the mitochondrial respiratory chain (Adapted from Huang *et al.,* 2009)

### 3.8.1.2 Reactive oxygen species and gene transcription

Another suggested mechanism of action for LLLT is that it induces transcriptional changes in cells through the activation of several transcription factors (nuclear factor kappa B (NF-κB), p53 and hypoxia-inducible factor (HIF) -1 brought about by changes in cellular redox state (Figure 3.7). LLLT is able to stimulate such reaction in cells through the boosting of oxygen metabolism leading to the production of ROS, a natural by-product and a chemically active molecule that plays an important role in evoking cellular signalling, regulation of cell cycle progression, enzyme activation, and nucleic acid and protein synthesis (Hashimi *et al.,* 2010; Huang *et al.,* 2009).

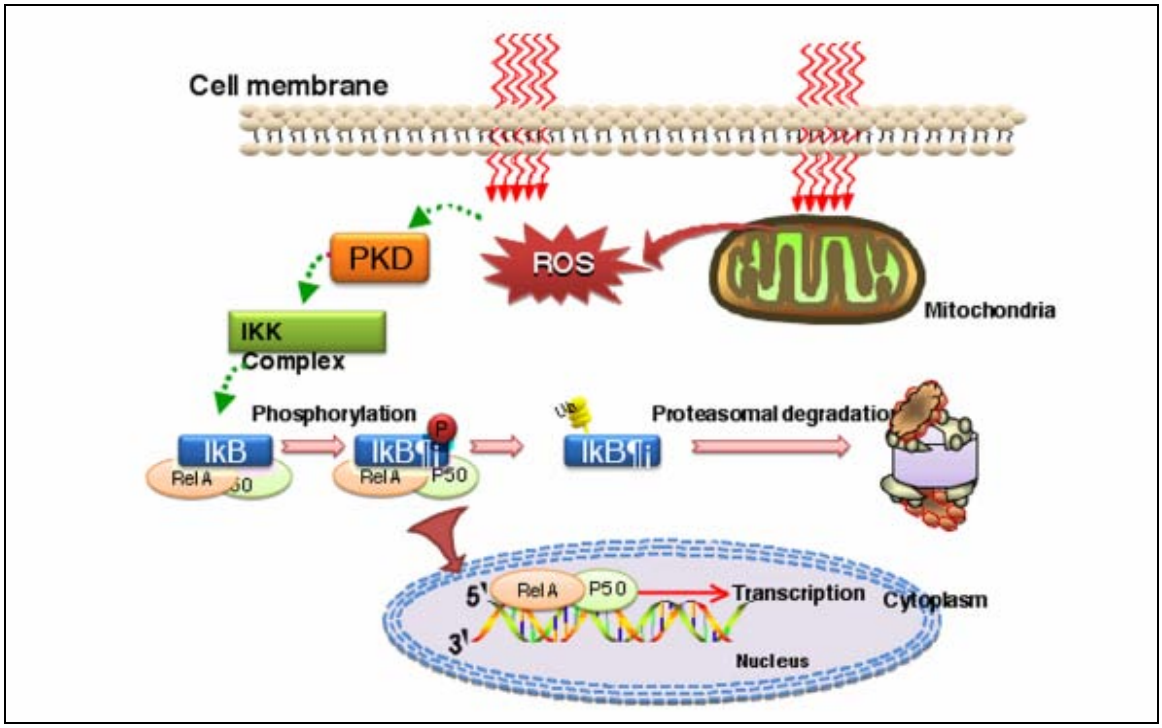


Figure 3-7 Diagrammatic illustration of reactive oxygen species (ROS) created due to the effects of LLLT on mitochondria, which could trigger the redox-sensitive transcription factor NF-κB (relA-p50) through protein kinase D (PKD) (Adapted from Huang *et al.,* 2009)

### 3.8.1.3 Mitochondrial respiration and ATP

There is strong evidence to suggest that LLLT acts on the mitochondria to increase ATP production. ATP is a form of cellular energy generated by oxidative phosphorylation of molecules by the mitochondria. When cells are exposed to a laser, the mitochondria and cell membrane traps the photon from the laser in the form of photonic energy, using the cytochromes inside the mitochondria. The photonic energy is transformed to chemical kinetic energy inside the cell, leading to alterations in membrane permeability as well as enhanced signalling between mitochondria, nucleus, and cytosol, thereby resulting in intensified oxidative metabolism to produce more ATP. The greater oxidative metabolism encourages cell metabolism and activation of signalling pathways necessary for significant cell migration, cell mitosis, and cell proliferation, which are required for normalisation of cell function, pain relief, and wound healing (Chuang *et al.,* 2012; Hashimi *et al.,* 2010; Huang *et al.,* 2009).

### 3.8.2 Evidence for effectiveness of LLLT in musculoskeletal conditions

Several studies have been published regarding LLLT for musculoskeletal conditions. The first clinical trial testing LLLT in musculoskeletal pain to investigate the effects of LLLT on rheumatoid arthritis was published in 1980 by Goldman *et al.* (de Almeida *et al.,* 2012; Gur *et al.,* 2004). According to de Bie *et al.* (1998), the first RCTs were published in 1981 by Gallachi *et al.,* who described the effects of laser therapy in the treatment of cervical and lumbar pain, and the study conducted by Lewith and Machin (1981), who evaluated the effects of infrared stimulation of local trigger points on the pain caused by cervical OA.

Although LLLT has been available for nearly three decades, this modality remains controversial (Bjordal *et al.,* 2008). A number of clinical trials have been performed with LLLT to treat a variety of musculoskeletal conditions, and they have reported positive effects in the treatment of conditions such as in rheumatoid arthritis (Johannsen *et al.,* 1994, Juhl, 2006), fibromyalgia (Gur *et al.,* 2002a; Gur *et al.,* 2002b; Panton *et al.,* 2012), low back pain (Gur *et al.,* 2003b), neck pain (Chow *et al.,* 2006; Gur *et al.,* 2004), and epicondylitis (Bjordal *et al.,* 2008). Nevertheless, positive results have been countered by numerous negative clinical trial results such as in painful musculoskeletal pathologies; for example, epicondylitis (Krasheninnikoff *et al.,* 1994), plantar fasciitis (Basford, 1998), and myofascial pain (Thorsen *et al.,* 1992). Furthermore, a meta-analysis conducted by Gam (1993) on the effect of LLLT on musculoskeletal pain showed that LLLT has no effect on musculoskeletal pain syndromes.

Likewise, the clinical efficacy of LLLT in the treatment of KOA is still debatable in terms of conflicting results. Many clinical trials have reported significant improvement (Alfredo *et al.,* 2011; Gur *et al.,* 2003a; Hegedus *et al.,* 2009; Shen *et al.,* 2009; Stelian

*et al.,* 1992), whereas others have failed to show such an effect (Bulow *et al.,* 1994; Tascioglu *et al.,* 2004; Trelles *et al.,* 1991; Yurtkuran *et al.,* 2007). Brosseau *et al.* (2004) conducted a meta-analysis to determine the effectiveness of laser therapy for OA of the hand, knee, and hip. Of the 144 potential articles, 7 studies met the inclusion criteria. In those studies, 184 patients were randomised to laser and 161 patients to placebo laser. The analysis found no difference between the effects of the laser and the placebo on pain.

Previous conflicting and negative results of published clinical trials regarding LLLT can be attributed to several factors and reasons. One of these reasons, the lack of standardization and the great variety of research methodologies used in terms of dosimetry, such as inadequate or excessive energy delivered, irradiation of an insufficient area of the pathology, inappropriate anatomical treatment location, treatment timing and repetition, pulsing, polarization, and concurrent patient medication (Alfredo *et al.,* 2011; de Paula Eduardo *et al.,* 2010; Hashmi *et al.,* 2010; Huang *et al.,* 2009). An ideal dose is required to obtain an optimal response, whereas lower dose rates present no significant results, and high dose rates present inhibitory effects; the effect of LLLT is dose dependent (Almeida-Lopes *et al.,* 2001; Bjordal *et al.,* 2008). Another reason is that the mechanisms of action of LLLT found at the molecular, cellular, and tissue levels remain uncertain (Hashmi *et al.,* 2010). Furthermore, lack of proper scientific training by the authors and lack of knowledge of photobiology could be another reason for conflicted results of published clinical trials regarding LLLT (Smith 2010).

It has been believed that LLLT represented by red or NIR light without any thermal effect produces the most significant responses *in vivo* and, consequently, is the best in terms of its photo-biological response (Rojas and Gonzalez-Lima, 2011). The main reason for using the red and NIR spectral region is the fact that haemoglobin, as photo-

acceptor or chromophore, does not absorb in this region, and light can penetrate deep into living tissue. Despite the wide use of LLLT in clinical practice and research and despite the fact that various mechanisms of its effect have been proposed, its mechanism remains not fully understood (Fukuda *et al.,* 2011; Gao and Xing 2009; Zhang *et al.,* 2009).

At the cell membrane of target cells, light photons are absorbed by photo-acceptors, where photonic energy is converted to chemical energy within the cell. Mitochondrial respiratory chain components are thought to be the principal photoreceptors of red and NIR light, and they play an important role in energy generation and metabolism (Gao and Xing, 2009; Hashmi *et al.,* 2010; Huang *et al.,* 2009). When photons are absorbed by the mitochondria; they stimulate more ATP and ROS and increase ribonucleic acid (RNA), protein synthesis, reactive intracellular calcium and release of nitric oxide (NO) (Al Ghamdi *et al.,* 2011; Gao and Xing 2009; Hashmi *et al.,* 2010; Huang *et al.,* 2009; Rojas and Gonzalez-Lima 2011). As a result of these reactions, the application of LLLT produces analgesic and anti-inflammatory effects and stimulates healing and the enhancing of fibroblasts and bone cells (de Andrade *et al.,* 2012).

When human soft-tissue is injured or traumatized, it releases chemical mediators, including prostaglandins, serotonin, histamine, substance P, and other inflammatory chemicals, which ultimately promote pain (Lee *et al.,* 2011). Although LLLT is clinically used to relieve pain, the mechanism by which it reduces pain is still not clear. Pain relief can occur as an inhibition of nociceptive signals at the peripheral nerves or/and as a result of anti-inflammatory, collagen proliferation, and circulation enhancement resulting from exposure to LLLT (Bjordal *et al.,* 2006; Gur *et al.,* 2004 Tascioglu *et al.,* 2012). Increase in ATP production as well as enhanced redox systems of the cell as a result of treating by LLLT have been shown to restore neuronal membranes and decrease pain transmission (de Paula Eduardo *et al.,* 2010). It has also

been demonstrated that LLLT induces analgesia by modulating inhibition of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), modulating nerve transmission and increasing endorphin and serotonin release (Abrisham *et al.,* 2011; Fulop *et al.,* 2010).

The anti-inflammatory effect of LLLT has been found in laboratory tests through the reduction of PGE2 and inhibition of COX-2 (Bjordal *et al.,* 2006; Sakurai *et al.,* 2000). Suppression of the activity of COX-2 enzyme reduces oedema formation and hyperalgesia (Pallotta *et al.,* 2012). In a review undertaken by Lopes-Martins *et al.* (2007), the authors concluded that LLLT has an anti-inflammatory effect. Pallotta *et al.* (2012) found that LLLT operating at 810 nm markedly reduced the signs of inflammation.

One of the important and interesting effects of using LLLT, is its ability to stimulate reparative properties in human cartilage. However, studies on the laser treatment of cartilage injury have produced divergent results (da Rosa *et al.,* 2012). It has been reported that several *in vitro* studies have shown that LLLT at certain wavelengths and certain combinations may stimulate fibroblast proliferation (de Paula Eduardo *et al.,* 2010). Young *et al.* (1989) found that wavelengths from 660 nm to 870 nm encourage macrophages to release factors that stimulate fibroblast proliferation, whereas an 880 nm wavelength inhibits the release of these factors. Nevertheless, da Rosa *et al.* (2012) found in their study on experimental models of OA, an AsGaAl laser with a wavelength 808 nm proved more effective in the repair of cartilage injury, leading to the stimulation of angiogenesis as well as a reduction in inflammatory exudate. The action of LLLT could have a direct bio-stimulatory effect on fibroblasts and trigger the production of collagen (Ng *et al.,* 2004).

It has been concluded that LLLT has a positive bio-modulator effect on the healing of bone defects and on bone regeneration (Kawasaki and Shimizu, 2000; Luger *et al.,* 1998; Merli *et al.,* 2005). Several *in vivo*, *in vitro*, and clinical trial studies have demonstrated the positive effects of photobiostimulation on cell proliferation, increased microcirculation, vascular neo-formation, and the stimulation of collagen production by fibroblasts and bone repair (de Andrade *et al.,* 2012; da Rosa *et al.,* 2010). Stein *et al.* (2005) demonstrated that the He-Ne laser (632.8 nm) can promote significant proliferation and differentiation of human osteoblasts (increasing the accumulation of calcium and promote bone repair) *in vitro*. Gerbi *et al.* (2008) demonstrated that the GaAlAs laser (830 nm) is effective in accelerating the healing process of bone injuries. Interestingly, the effect of LLLT and the response of the tissue *in vivo* are directly correlated to stress conditions, and thus it is lacking when applied to healthy tissue (Almeida-Lopes *et al.,* 2001).

## 3.8.3 Studies examining the efficacy and effect of LLLT

### 3.8.3.1 Evidence-based in literature:

In medicine and healthcare studies, finding and using research results to support researchers' professional decisions is based on the principle of evidence-based medicine (EBM) (Makela and Witt, 2005). Sackett *et al.* (2000) defined EBM as 'the explicit, judicious, and conscientious use of current best evidence from health care research in decisions about the care of individuals and populations'. Sackett (1996) proposed a standardized system of interpreting medical research, with Level I being the highest (prospective, randomised, blinded controlled trials) and Level V being the lowest (case reports). In another classification for EBM, presented in Barbier and Hoogmatens (2004) review article, the lowest level of evidence (level 5) is the expert opinion, whereas the systematic review and the meta-analysis provides the highest (level 1

evidence) (Figure 3.8). However, RCT, as in the current study, reaches a 1B level of evidence, especially blinded studies. Furthermore, there are many evidence databases that have been developed, such as the physiotherapy evidence database (PEDro), which was developed specifically for use in physiotherapy as a means of rating the quality of published RCTs (PEDro 2013).

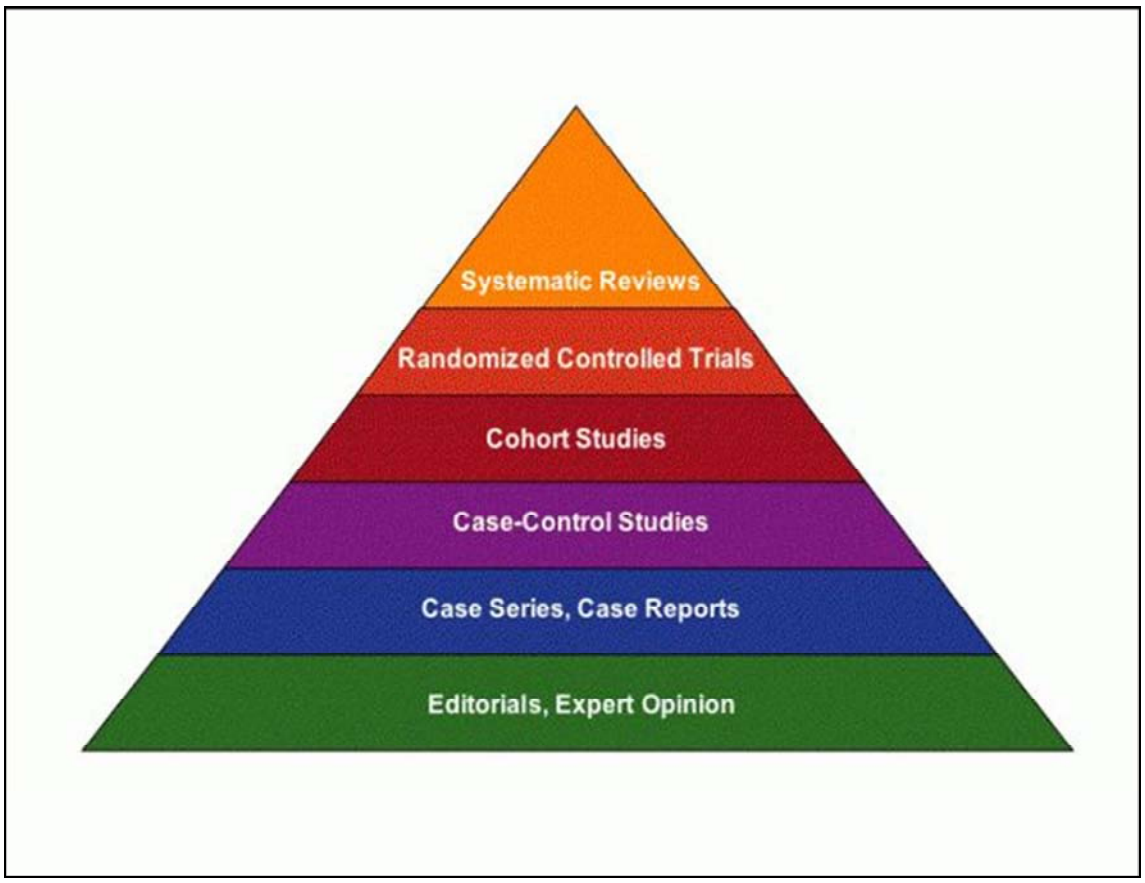


Figure 3-8 Level of Evidence Pyramid (adapted from http://gollum.lib.uic.edu/nursing/node/12)

Moreover, consideration of the strengths and weaknesses of a research article is important when assessing the usefulness and validity of research findings. Therefore, clinicians must be able to select and appraise scientific literature that is relevant to their field (Young and Solomon, 2009). According to Young and Solomon (2009), critical appraisal has been defined as the '. . . application of rules of evidence to a study to assess the validity of the data, completeness of reporting, methods and procedures, conclusions, compliance with ethical standards, etc. The rules of evidence vary with

circumstances'. Finally, for the current study, the quality of included studies were assessed according to information and recommendations derived from evidence databases such as PEDro and level of evidence pyramid (Figure 3-8), in addition to a review done by Young and Solomon (2009), which were all mentioned in the current section.

#### 3.8.3.2 Studies examining the efficacy and effect of LLLT in the treatment of KOA when applied on APs

Laser acupuncture or using LLLT as an alternative to metal needles for the stimulation of APs or musculoskeletal trigger points has been promoted for almost three decades. Recent studies have clearly shown that laser acupuncture can be successfully used as an alternative to metal needles for effective AP treatment. Furthermore, LLLT is safer and it requires less time than needle AP; with it, patients can avoid the pain and psychological fear of traditional AP (Baxter *et al.,* 2008; Lin *et al.,* 2012; Litscher and Opitz, 2012).

In 1979, Zhou, a surgeon in China, used laser acupuncture as a type of controlled anaesthetic method for dental indications; the author performed more than 10,000 tooth extractions with this laser acupuncture anesthesia. In the western world, it was a Canadian, Friedrich Plog, who pointed out the usefulness of laser acupuncture, and tested lasers instead of needle acupuncture in 1973 in this context (Litscher and Opitz 2012). Laser acupuncture is promoted as inherently safer than needle acupuncture and as a non-invasive treatment (see chapter 1). APs have been shown to play very important roles in acupuncture therapy, where they have lower electrical resistance than their surrounding tissues (Liu *et al.,* 2008).

Baxter *et al.* (2008) conducted a systematic review to evaluate RCTs used in laser acupuncture as a primary intervention. Relevant studies (n = 18) were identified; 9

studies were undertaken to investigate the effectiveness of laser acupuncture in the treatment of myofascial pain or musculoskeletal trigger points affecting the neck, shoulder, and thoracic or lumbar spine. Seven of these studies reported positive outcomes in favour of laser acupuncture. However, this systematic review included no studies conducted for treating OA.

During this search via search engines, to find the studies in which LLLT was applied on APs, only two published studies were found. One was conducted by Yurtkuran *et al.* (2007), and the other one was a pilot study carried out by Shen *et al.* (2009).

Shen *et al.* (2009) carried out a randomised, single-blind and placebo-controlled trial (RSBCT) to assess the efficacy and safety of combined 10.6 μm and 650 nm laser irradiation on patients with KOA. Forty patients were randomly assigned, via Excel 2000 software-generated randomised numbers, either to a laser group or a placebo group. The laser group (20 patients, 18 women and 2 men) received a combined active laser therapy (semiconductor laser generates an ~ 0. 65–0.66 μm red light transmitted by quartz-glass light fibres with an output power of 36 mW, and a $CO_2$ laser, which generates a 10.6 μm light transmitted by a silver halide light fibre with an output power of 200 mW and set to pulse with a frequency of 40 Hz, with a single beam 2 mm in diameter and non-contacted with the skin, with 2 cm distance and 20 minutes of treatment time). Laser irradiation was applied to Dubi or Xiyan (ST35) AP, which is located in the depression on the lateral side of the patella and the patellar ligament; for more details of this AP see Figure 5.7 and Table 5.2. Participants in the placebo laser group received the same procedure, but the laser device was inactivated. Both groups were treated 3 times per week, for 4 weeks. The subjects were evaluated at baseline and week 2.

The primary outcomes of the study were pain, stiffness, and function by WOMAC. The 4 week assessment could not be analysed because some patients dropped out (2 from the active laser group and 11 from the placebo group). Consequently, the authors of the study stated that they could not conclude that the positive result of the study was due to a therapeutic effect or a placebo effect, as a result of the high dropout rate of the placebo group.

Yurtkuran *et al.* (2007) conducted a RDBCT to investigate the effects and minimum effective dose of laser acupuncture on patients with KOA. Fifty-five patients were randomly assigned either to a laser group or a placebo group. Laser group received active laser therapy (GaAs infrared laser 904 nm with 10 mW/cm$^2$ power density, 4 mW output power, 0.4 cm$^2$ spot size, 0.48 J dose per session, and 120 s treatment time on the median side of the knee to the Yinlingquan AP spleen 9 (SP9), which is located on the inferior border of the medial condyle of the tibia, in the depression between the posterior border of the tibia and the gastrocnemius muscle, for more details of this AP see Figure 5.7 and Table 5.2. The placebo group received a placebo laser therapy (0 J/cm$^2$, red light emitted). Patients in both groups received knee exercise and all treatments were applied once a day for 20 minutes, 5 days a week for a total of 2 weeks (10 treatment sessions).

The subjects were evaluated at baseline, after the treatment, and at the 12th week. The main outcome measures were WOMAC and VAS to evaluate pain and function, Nottingham Health Profile (to evaluate QoL: perceived physical, social, and emotional health), 50 foot walking time (patients were asked to walk a standard distance as fast as possible, and then the duration was recorded in seconds), KC by standard tape measure (cm), medial tenderness score (MTS) by using a pressure algometry, a technique used to evaluate pressure pain threshold, the minimal amount of pressure that produces pain, where the most painful point was evaluated. The authors of the study concluded that

their application of LLLT was effective only in reducing the periarticular swelling when compared with the placebo treatment.

Although the studies by Shen *et al.* (2009) and Yurtkuran *et al.* (2007) appear to be rigorous, as both were conducted RCBTs (level of evidence IB, according to 5-levels EBM (Barbier and Hoogmatens 2004); Shen *et al.*'s study appears to be less rigorous because it was conducted in a single-blind fashion rather than double-blind as in Yurtkuran *et al*.

Both studies have a strong homogeneity of the subjects due to the rigorous inclusion and exclusion criteria; however, this homogeneity could be affected in terms of gender distribution (4 men and 36 women in Shen *et al.* and 2 men and 53 women in Yurtkuran *et al.*), in particular, because the discrepancies between studies still stand in who has a higher pain threshold and pain tolerance, women or men (Defrin *et al.,* 2009). The consequence of this heterogeneity is that using pain as a main outcome measure for the majority of LLLT studies could be affected. Both studies used well-known validated and reliable outcome measurement tools; however, Yurtkuran *et al.*'s study is still more rigorous in terms of using a mixture of subjective (e.g. WOMAC and VAS) and objective (e.g. 50-foot walking time and MTS) tools, whereas Shen *et al.* used only subjective tools (WOMAC and patients' global assessment).

Both studies suffer from limitation because only one AP was irradiated, while in acupuncture and other laser acupuncture studies, researchers usually use more APs, as will be highlighted in the next chapter. Furthermore, in laser acupuncture trials more APs should be added to make the treatment more comparable to clinical acupuncture trials. Shen *et al.*'s study suffers from its short follow-up period (4 weeks), and a high dropout rate (13 of 40 participants), especially among participants in the placebo group, whereas Yurtkuran *et al.*'s study has a reasonable follow-up period (12 weeks) and a

reasonable sample size (55 participants). However, Shen *et al.*'s study is a pilot study, and the authors reported some of the aforementioned limitations. Likewise, Yurtkuran *et al.* reported that the applied doses were less than the doses recommended by the World Association for Laser Therapy (WALT) for musculoskeletal diseases.

#### 3.8.3.3 Studies examining the efficacy of LLLT in the treatment of KOA when applied on different site other than APs

Several studies have been conducted to investigate the efficacy or the effect of using LLLT for treating patients with KOA. These studies are discussed in details in the following pages, and are summarized in Table (3.3) below, in order to facilitate comparison between them.

Rayegani *et al.* (2012) conducted a RDBCT to assess the effects of LLLT on patients with KOA and compared LLLT to therapeutic ultrasound. Sixty-two patients were selected for the examinations, but only thirty-seven completed the study, patients were randomly assigned to receive either LLLT, placebo LLLT or ultrasound. Laser group (12 patients: 10 women and 2 men) received active laser therapy (diode laser with 880 nm) (see Table 3.3), 8 points on the affected knee were irradiated with a total dose of 24 $J/cm^2$ per session; irradiation was done in contact with the skin). The placebo group (13 patients: 12 women and 1 man) was treated with an ineffective laser probe (power 0 mw) and with the same method. The ultrasound group (12 patients: 11 women and 1 man) received ultrasound (given in a pulsed method, 1 MHz, with a dose of 1.5-2 $W/cm^2$, for 5 minutes per knee). All patients received a common treatment, including acetaminophen (up to 2 grams per day) and medical advice for lifestyle modification and exercise.

All treatments were applied five times a week over a period of two weeks. The subjects were evaluated at baseline, 1 month, and 3 months after completing the therapy. The main measurements were pain, function, and disability, using VAS and WOMAC. The

result of the study showed that LLLT reduces pain, joint stiffness, and disability in KOA and is superior to placebo and ultrasound. Furthermore, the positive effects of active LLLT still persisted three months after treatment, except for joint stiffness.

Alfredo *et al.* (2011) conducted a RDBCT to estimate the effects of LLLT on patients with KOA. Forty-six patients were randomly assigned either to a laser group or a placebo laser group. Forty patients completed the study, the laser group (20 patients: 15 women and 5 men) received active laser therapy (GaAs infrared laser 904 nm) over the joint line onto five points of the synovial region of the medial side of the knee and in 4 points at the lateral side, total dose per knee was 27 J per treatment), in addition to exercises. The placebo group (20 patients: 16 women and 4 men) received identical procedures as did the active laser group but without emission of energy. All treatments were applied 3 times per week for 3 weeks following initial assessment (9 treatment sessions by laser) and exercises were provided during 8 weeks, with 3 sessions a week, and each session lasted 45 minutes.

The subjects were evaluated at baseline, after laser treatment (3 weeks), and after 11 weeks following the end of exercise therapy. Main measures were pain via VAS, an activity using the WOMAC, functionality using the Lequesne questionnaire, range of motion with a universal goniometer, and muscular strength using a dynamometer. The authors of the study found a positive effect of LLLT, and they stated that the application of LLLT 3 times per week for 3 weeks can assist in the execution of exercises in patients with KOA, and that the combination of laser and exercise can improve the pain, function, and activities of those patients.

Hegedus *et al.* (2009) conducted a RDBCT to investigate the effect of LLLT on pain and possible microcirculatory changes in patients with KOA. Thirty-five patients were randomly assigned to receive either active or placebo laser. Only 27 patients (22 women

and 5 men) completed the study (18 were in the laser group and 9 were in the placebo group). Treatments were delivered twice a week over a period of 4 weeks with a GaAlAs laser ( 830nm), 8 points at the affected knee were irradiated with a total dose of 48 J/cm$^2$ per session; irradiation was with contact with the skin). The same machine with a placebo probe (power 0.5mW) with the same appearance and display was used in the placebo group.

Outcome measurements were subjective (pain via VAS), semi-objective (pressure sensitivity using the Ritchie index (facial expressions), and objective (joint flexion in degrees via Domjan-Balint mobimet, KC (cm), and microcirculatory changes via thermography by AGA infrared camera). Patients were evaluated at baseline, weekly after the second treatment at the same time each week, at 2 weeks and 2 months after completing the therapy. The result of the study showed that there was improvement in all outcome measures in the active laser group compared to baseline, but not in the placebo group. The authors of this study found the positive effect of active LLLT still persisted 2 months after treatment. They concluded that LLLT is an effective treatment for patients with painful KOA, at least for the short-term.

Tascioglu *et al.* (2004) conducted a RSBCT to evaluate the analgesic effect of LLLT in patients with KOA. Sixty patients were randomly assigned to three groups, and the active laser was a GaAlAs diode laser (Endolaser 476, Enraf Nonius, Netherlands). The treatment was applied to five painful points at both sides of the affected knee. Group I (20 patients: 14 women and 6 men) received active laser therapy (2 minutes irradiation/ per point, dose 3 J/point, total dose per treatment 15 J/ point). Group II (20 patients: 15 women and 5 men) received active laser therapy (1 minute irradiation/ per point, dose 1.5 J/ point, total dose per treatment 7.5 J/ point). Group III (20 patients: 13 women and 7 men) received the same procedures as the active laser groups did, but with an inactivated laser beam.

Outcomes measurement tools were WOMAC and VAS. Patients were evaluated at baseline, 3 weeks, and 6 months. All treatments were applied once a day, 5 days a week, for a total of 10 days. The result of the study showed that no significant statistical difference was observed within the groups or between the groups at any time between the active laser treatments given at two different dosages and the placebo group at any time.

Gur *et al.* (2003a) conducted a RDBCT that was designed to evaluate the efficacy of infrared LLLT in painful KOA and compared two different laser therapy regimes with regards to some parameters, such as power output, stimulation time, and pulsing frequency. Ninety patients (72 women and 18 men) were randomly assigned to 3 treatment groups.

The laser device used in this study was a GaAs infrared laser (904 nm). The same unit was used for the placebo treatment, which emitted no laser beam. The treatment was applied to two points at the antero-lateral and antero-medial portals of the affected knee. In group I, 30 subjects (25 women and 5 men) received active laser (GaAs infrared laser, 5 minutes irradiation, 3 J total energy, and 30 J accumulated dose; i.e. 15 J/point). In group II, 30 subjects (23 women and 7 men) received an active laser (2 J total energy, and 20 J accumulated dose; i.e. 10 J/point. In Group III, 30 subjects (24 women and 6 men) received the placebo laser; the laser emitter was similar to the infrared emitter in appearance, but it did not emit light. In all groups, patients were given an exercise therapy programme over 14 weeks. All patients received a total of 10 treatments with active or placebo laser for 2 weeks, and exercise continued for 14 weeks.

The outcome measurement tools used were VAS, WOMAC, goniometry, duration of morning stiffness in minutes, and painless walking distance in meters. Follow-up measures were assessed at baseline and at 4, 8, and 12 weeks after the last therapy. The

results of the study showed that the different regimes of LLLT which were applied on patients with KOA in the study were a safe and effective treatment. Furthermore, the authors of the study concluded that significant improvements in some outcome measures starting from week 10 in the placebo laser group may have arisen from the exercise therapy applied rather than the placebo effect.

Bulow *et al.* (1994) investigated the effect of LLLT on patients with chronic KOA with periarticular tender points by conducting a RDBCT. Twenty-nine patients (24 women and 5 men) were randomly assigned to treatment with either laser (14 patients) or placebo laser (15 patients). The study was divided into pre-treatment, treatment, post-treatment periods, of 3 weeks each. Outcome measures were pain via fill in a questionnaire form based on the level of pain, palpation tenderness by using a pressure of approximately 4 Kg, and isokinetic quadriceps strength via a Kin-COM dynamometer.

The active laser was a GaAlAs infrared laser with a wavelength of 830 nm. Each patient participated in the study for 9 weeks. Patients received a total of 9 treatments, which were started in weeks 4, 5, and 6 (period 2), each for 15 minutes and applied to periarticular tender points, for 2–4 treatments a week. Each tender point received between 1 and 3 minutes of irradiation, and the dose varied between 1.5 and 4.5 J each. The dose per treatment of active laser was 22.5 J, and the accumulated dose for all 9 treatment sessions was 202.5 J.

The result of the study showed that no significant differences were found between the two groups with respect to pain and muscle strength. A significant reduction was noted in the palpation tenderness in the laser group when it was compared before and after the treatment. Within each group, there was a small insignificant change in favour of pain. The authors concluded that the overall assessment showed no significant differences

between the participants who were treated with the active laser and those who were treated with the placebo laser.

Stelian *et al.* (1992) investigated the efficacy of LLLT on pain and disability in elderly patients with degenerative KOA. The study was designed as a partially RDBCT comparing He-Ne red laser with a wavelength of 633 nm, a GaAlAs infrared laser with a wavelength of 830nm, and placebo laser light emitters. The study was conducted in a partially double-blinded design (double-blinded fashion for infrared and placebo emitters but not for the red emitter where light is visible). Fifty patients (34 women and 16 men) were randomly assigned to 3 groups. Group I (n =15) received red laser), Group II (n =18) received infrared laser, and Group III (n =17) received placebo laser, which was the same as the infrared emitter in appearance but did not emit light. Each patient received 15 minutes of intervention applied at both sides of the knee twice a day for 10 days. Every treatment was composed of 7.5 minutes of continuous wave application and 7.5 minutes of pulse treatment. The outcome measures were pain level and functional disability, which were evaluated by a Short-Form McGill Pain questionnaire (SF-MPQ), Present Pain Intensity (PPI) questionnaire, and VAS, Disability Index questionnaire (DIQ). The follow-up measures were assessed at baseline and on the 10th day of therapy.

The result of the study showed significant pain reduction and functional improvement in the red laser and infrared laser light groups, but not in the placebo laser group, in all three pain evaluation methods. The authors of the study concluded that the short-time application of LLLT is effective in pain relief and in improvement of functional ability in elderly patients with degenerative KOA.

Trelles *et al.* (1991) conducted a non-randomised and uncontrolled study to investigate the efficacy of LLLT in patients with KOA. Forty patients (24 women and 16 men)

were treated by active GaAlAs laser with a wavelength of 830 nm at 4 points around the patella, which were irradiated for 60 s each, with the energy density of 18 J/cm$^2$ per point, a total of 72 J/cm$^2$ per session, and with light contact technique). Treatment was administrated 3 sessions per week for 4 weeks. Radiological changes, pain scores, and joint mobility were the outcome measurement tools of the study. Assessments were made at the baseline, immediately after last treatment, and at 4 months after the final LLLT session. The result of the study showed that 33 patients (82%) reported significant improvement of pain and recovery of articular joint mobility. The authors concluded that this treatment is a safe, effective, and non-invasive alternative to conventional surgical and medical treatment modalities for patients with KOA.

**Table 3-3 Summary for some related studies examining LLLT for the treatment of KOA**

| Study | Design | Patients (n =) | Laser type & (parameters) | Endpoint assessment | Mean baseline of primary outcome (VAS) | Endpoint mean and/or mean difference between groups; p value | Other outcomes | Result of the end point assessment (between groups) |
|---|---|---|---|---|---|---|---|---|
| Rayegani *et al.* (2012) | RDBCT | (*n* = 62), 37completed (33 F, 4 M) | **Laser parameters:** Diode 880 nm continuous wave **Power output:** 50 mW **Spot size:** 1 $mm^2$ **Dose:** 6J point X 8 points X 10 sessions | 3 months | Active group: mean= 6.3 Control group: mean= 5.2 | Active group: mean= 4.8 Control group: mean= 4.4 | WOMAC | Pain reduced and the quality of life improved |
| Alfredo *et al.* (2011) | RDBCT | (*n* =46), 40 completed (31 F, 9 M) | **Laser parameters:** GAAS 904 nm **Pulsed:** 700 Hz **Power output:** 60 mW **Spot size:** 0.5$cm^2$ **Dose:** 3J point/ 50 s X 9 points X 10 sessions | 11 weeks | Active laser group: mean= 5.32 Control group: mean= 3.54 | Active group: mean= 2.58 Control group: mean= 2.30; p = 0.120 | WOMAC Lequesne questionnaire, goniometer, dynamometer (muscular strength) | Pain reduced; function and activities improved |
| Hegedus *et al.* (2009) | RDBCT | (*n* = 27), (22 F, 5 M) | **Laser parameters:** GaAlAs 830 nm Continuous wave **Power output:** 50 mW **Spot size:** 0.5$cm^2$ **Dose:** 6J point X8 points X 8 sessions | 2 months | Active group: mean= 5.75 Control group: mean= 5.62 | Active group: mean= 1.18 Control group: mean= 4.12 | Ritchie index (pressure sensitivity), Domjan-Balint mobimet (ROM), KC, AGA infrared camera | Pain reduced and microcirculation improved (microcirculatory changes) |
| *n,* patients number; F, female; M, Male; p, p value | | | | | | | | |

| Study | Design | Patients (n =) | Laser type & (parameters) | Endpoint assessment | Mean baseline of primary outcome (VAS) | Endpoint mean and/or mean difference between groups; p value | Other outcomes | Result of the end point assessment (between groups) |
|---|---|---|---|---|---|---|---|---|
| Shen *et al.* (2009) | RSBCT | (n = 40) (36 F, 4 M) | **Laser parameters:** Combined 10.6 μ m $Co_2$ and semiconductor 650 nm **Power output:** 200 mW **Pulsed:** 40 Hz **Spot size: 2mm** **Dose:** not specified – AP ( ST35) X 20 mins X 12 sessions | 2 weeks | _ | _ | WOMAC Patients' global assessment; assessment of adverse effects; medication usage; masking effectiveness | Pain reduced |
| Yurtkuran *et al.* (2007) | RDBCT | (n = 55), (53 F, 2 M) | **Laser parameters:** GaAs 904 nm **Pulsed:** 200 nanosecond **Power output:** 4 mW **Spot size:** 0.4 $cm^2$ **Dose:** 0.48J point X AP (SP9) X 120s X 10 sessions | 12 weeks | Active group: mean= 6.47 Control group: mean= 6.06 | Active group: mean= 5.58 Control group: mean= 4.81; p = 0.50 | WOMAC, Nottingham Health Profile (NHP), 50-foot walking, Medial Tenderness Score (MTS), KC, | No significant differences between groups were observed, except regarding KC. |
| Tascioglu *et al.* (2004) | RSBCT | (n =60), (42 F and 18M) | **Laser parameters:** GaAlAs 830 nm **Power output:** 50 mW **Spot size:** 1 mm **Dose:** (Active group I): 3J point X 5 points X 2 mins point X 10 sessions; (Active group II): 1.5J point X 1 min point X 10 sessions; (Control group): placebo | 6 months | Active group I: mean= 6.80 Active group II: mean= 6.57 Control group: mean= 6.39 | Active group I: mean= 6.68 Active group II: mean= 6.18 Control group: mean= 6.20, p > 0.05 | WOMAC | Regarding to VAS and WOMAC, there were no significant differences were observed between groups. |

*n,* patients number; F, female; M, Male; p, p value; _ , VAS was not used in the relevant study.

| Study | Design | Patients (n =) | Laser type & (parameters) | Endpoint assessment | Mean baseline of primary outcome (VAS) | Endpoint mean and/or mean difference between groups; p value | Other outcomes | Result of the end point assessment (between groups) |
|---|---|---|---|---|---|---|---|---|
| Gur *et al.* (2003) | RDBCT | (*n* = 90), 72 F, 18 M) | **Laser parameters:** GaAs 904 nm<br>**Power output:**<br>Active group I : 10-mW average power,<br>Active group II : 11.2-mW average power<br>**Spot size:** 1-$cm^2$<br>**Dose:** ( Active group I): 3J point X 2 points X 5 mins point X 10 sessions;<br>( Active group II ): 2J point X 3 min point X 10 sessions;<br>(Control group): placebo | 12 weeks | Active group I : mean= 7.32<br>Active group II: mean= 7.44<br>Control group : mean= 6.74 | Active group I : mean= 3.58<br>Active group II: mean= 3.80<br>Control group : mean= 4.30;<br>p > 0.05 | WOMAC, a goniometry, duration of morning stiffness in minutes, painless walking distance in (m). | Pain reduced and the quality of life improved. |
| Bulow *et al.* (1994) | RDBCT | (*n* =29), (24 F, 5 M) | **Laser parameters:** GaAlAs 830 nm<br>Continuous beam<br>**Power output:**<br>25 mW<br>**Spot size:** 0.28 $cm^2$<br>**Dose:** 1.5 - 4.5 J point X 5-15 points X 1-3 mins irradiation X 9 sessions | 9 weeks | _ | _ | Questionnaire form based on the level of pain, palpation tenderness by using a pressure of approximately 4 kg. | No significant difference was observed between groups. |

*n,* patients number; F, female; M, Male; p, p value; _ , VAS was not used in the relevant study.

| Study | Design | Patients (n =) | Laser type & (parameters) | Endpoint assessment | Mean baseline of primary outcome (VAS) | Endpoint mean and/or mean difference between groups; p value | Other outcomes | Result of the end point assessment (between groups) |
|---|---|---|---|---|---|---|---|---|
| Stelian *et al.* (1992) | Partially RDBCT | (*n* = 50), (34 F, 16 M) | **Laser parameters:** red laser and pulsed near infrared laser. Continuous & pulsed **Power output:** 18, 75, 25, and 270 mW **Spot size:** 2 $cm^2$ **Dose:** 7.5 mins of continuous wave & 7.5 mins of pulse treatment X both sides of the knee X 10 sessions | 10 days | Active group I : mean= 6.53 Active group II : mean= 7.16 Control group: mean= 6.23 | Active group I: mean= 3.33 Active group II : mean= 3.22 Control group : mean= 6.29; p < *0.05* | (SF-MPQ), DIQ, PPI | The pain relief period was significantly longer for the two laser groups in comparison to the placebo group. Pain reduced; function and activities improved. |
| Trelles *et al.* (1991) | Non randomised and non-controlled | (*n* =40), (24 F and 16 M) | **Laser parameters:** GaAlAs 830 nm Continuous beam **Power output:** 60 mW **Spot size:** 2 $cm^2$ **Dose:** 60 s of irradiation X 4 points X 8 sessions | 4 months | _ | _ | Radiological changes, joint mobility and KC | Pain and inflammation, reduced. |
| *n,* patients number; F, female; M, Male; p, p value; -, VAS was not used in the relevant study. | | | | | | | | |

Most of the previous studies discussed herein appear to be rigorous (level of evidence IB) in that they were conducted in a strong design RDBCT (Alfredo *et al.,* 2011; Bulow *et al.,* 1994; Gur *et al.,* 2003a; Hegedus *et al.,* 2009; Rayegani *et al.,* 2012) except for those by Stelian *et al.* (1992), which was designed as a partially RDBCT; Tascioglu *et al.* (2004), which was conducted in a single blinded fashion; and Trelles *et al.* (1991), which was conducted in a non-randomised and uncontrolled fashion. Although RDBCT has been described as a gold standard technique which has been accepted by medicine as an objective scientific methodology when ideally performed produces knowledge untainted by bias, Relf *et al.* (2008) reported that the blinding techniques used in RDBCT of laser treatment rely on staff cooperation and hence are subject to bias or interference and indicate significant deficiencies in the laser trial methodology.

The majority of the studies have a strong homogeneity of the participants due to their rigorous inclusion and exclusion criteria, although this homogeneity could be affected in terms of gender distribution. Most of these studies were on a sample of females rather with some balance between genders. As mentioned earlier, there are discrepancies with regards to pain threshold and pain tolerance between genders which could affect the pain measure as a main outcome measure in LLLT studies. All studies used at least one validated and reliable measurement tool; however, Alfredo *et al.* (2011), Hegedus *et al.* (2009), Bulow *et al.* (1994), and Gur *et al.* (2003a) used a mixture of subjective and objective outcome measurement tools, which made these studies more rigorous than others which used only subjective measurement tools, such as VAS and WOMAC (e.g. Rayegani *et al.* 2012 and Tascioglu *et al.* 2004). Lu *et al.* (2010) reported that subjective assessment tools are influenced by several factors, such as age and mental condition as in VAS, and/or influenced by some diseases other than OA, e.g. low back pain, depression, and fatigue as in WOMAC. Therefore, objective and precise assessment tools are required to fill this gap.

In all studies 4–8 points were irradiated at and around the knee joint except in the study by Gur *et al.* (2003a), in which only two points were irradiated, and in Stelian *et al.* (1992) where the laser irradiation was applied on both sides of the affected knee, but at no specific points. By using more irradiated points, the authors could add extra strength to their studies and make their treatment method more comparable to other similar clinical trials, especially those on acupuncture and other LLLT trials for treating KOA. Tascioglu *et al.*'s (2004) study has the longest follow-up period (6 months) among these studies, which might makes their results more rigorous. In contrast, Stalin *et al.* (1992) had the shortest follow-up period, which was on the 10th day (i.e. after the last treatment session).

Furthermore, Brosseau *et al.* (2004) conducted a meta-analysis (level I of evidence) to determine the effectiveness of laser therapy for OA of the hand, knee, and hip. Of the 144 potential articles, 7 studies met the inclusion criteria, and 184 patients were randomised to receive laser treatment, and 161 patients were randomised to undergo the placebo laser. The analysis found no difference between laser and placebo on pain.

The main limitation of this systematic meta-analysis is the heterogeneity of the included studies, including different dosages, wavelengths, site of application, and types of LLLT, and the authors found statistically significant heterogeneity ($p < 0.05$). Nevertheless, it has been reported by the Cochrane Library that this systematic meta-analysis was withdrawn from the library for two reasons. The first being that 'comments received have suggested the presence of a substantial number of additional trials claiming positive results that need to be reviewed, and that, if eligible, could affect the conclusions'. The second reason was that 'some errors made in the extraction of data from two trials were pointed out'. According to the Cochrane Library, these errors involved only 3 in over 100 figures and we note that replacing our calculations would not affect the conclusions of the review'.

On the contrary, Bjordal *et al.* (2003) conducted a systematic review (level 1 of evidence) of LLLT with location-specific doses for pain from chronic joint disorders. Eleven trials were included that involved 565 patients. LLLT within the suggested dosage range was administered to the knee joint in 4 studies. The result of this review indicated that LLLT with the suggested dose range significantly reduces pain and improves health status in chronic joint disorders in favour of the active LLLT group. The authors concluded that more and larger trials are needed to determine the optimal treatment procedures for LLLT and possible interaction with other therapies for chronic joint disorders.

As in Brosseau *et al.* (2004), this review is suffers from some limitations. The weakest point of this review is the heterogeneity in treatment procedures within the patient sample. The differences in numbers and frequencies of the treatment sessions, dosages, wavelengths, site of application and types of LLLT in addition to trial design could increase heterogeneity in results. The use of prohibited co-intervention drugs is also a factor that could increase the heterogeneity in results.

Two animal studies were conducted to investigate the effect of LLLT on knee arthritis. Pallotta *et al.* (2012) conducted a RCT to investigate the effect of LLLT (infrared, 810 nm, 100 mW output power, 0.028 $cm^2$ spot size area, power density of 5 $W/cm^2$, and the irradiation was performed with skin contact) in experimentally induced rat knee inflammation. Thirty male Wistar rats were used for the study. According to the results of the study, the authors concluded that laser radiation could be acting to modulate the inflammatory process and possibly stimulating the production of anti-inflammatory mediators.

The second study was conducted by da Rosa *et al.* (2012) to analyse the influence of LLLT in an experimental model of KOA. Thirty-six male adult Wistar rats were divided

into three groups. Group I received InGaAl LLLT (wavelength 660 nm, and 4 points at knee joint were irradiated). Group II received GaAlAs LLLT (wavelength 808nm at the same points used for group I). Group III received no treatment and served as the control group. The results of the study illustrated that the GaAlAs 808 nm laser proved to be more effective in the repair of cartilage injury in an experimental model of KOA as a consequence of the stimulation of angiogenesis as well as a reduction in inflammatory exudates.

# Chapter 4 Review of the literature of acupuncture

## 4.1 Background

Although the history of acupuncture dates back in China for several millennia, it has not lost its popularity; instead, it has gained popularity (Cabyoglu *et al.,* 2006). Acupuncture is an essential part of Traditional Chinese Medicine (TCM), which includes a variety of interventions such as moxibustion (burning herbs), herbal prescription, cupping, and Tai Chi exercise. Furthermore, it is among the best known forms of complementary and alternative medicine (CAM). Acupuncture is commonly practiced as a routine treatment in China, Japan, Korea, and Taiwan and, since the late 1970s, has gained popularity in the USA and the rest of the western world (Sierpina and Frenkel, 2005). The term acupuncture consists of two words from the Latin: *acus*, or needle and *puncture* or insertion (Cabyoglu *et al.,* 2006). Two different types of acupuncture therapy, manual acupuncture (MA) and electro-acupuncture (EA), are performed. EA uses an electrical current which is usually TENS (Lin and Chen, 2008). Moreover, Staud (2007) stated that APs can be manipulated in several different ways, including manual needling, electrical stimulation, heat (moxibustion), pressure (acupressure), and laser energy.

Acupuncture is characterised by the insertion and manipulation of fine, solid, usually stainless steel needles (usually 32 to 36 gauge) into selected body locations (APs, n = 365) along 12 meridians (channels of energy flow) located throughout the body, depending on the condition being treated (Sierpina and Frenkel, 2005; De Luigi, 2012). Although many references reported that the human body contains 365 APs and 12 meridians, Liu *et al.* (2008) stated that there are more than 2000 APs, which are nonuniformly distributed on the human body. Whereas, Ahn *et al.* (2008) cited from some previous studies that about 361 points are located on 14 main meridians. APs are thought to be linked to each other by meridians and are located at sites that have a high

density of neurovascular structures and are generally between or at the edges of muscle groups; these sites are less painful than random needle sticks into a muscle group (Sierpina and Frenkel 2005).

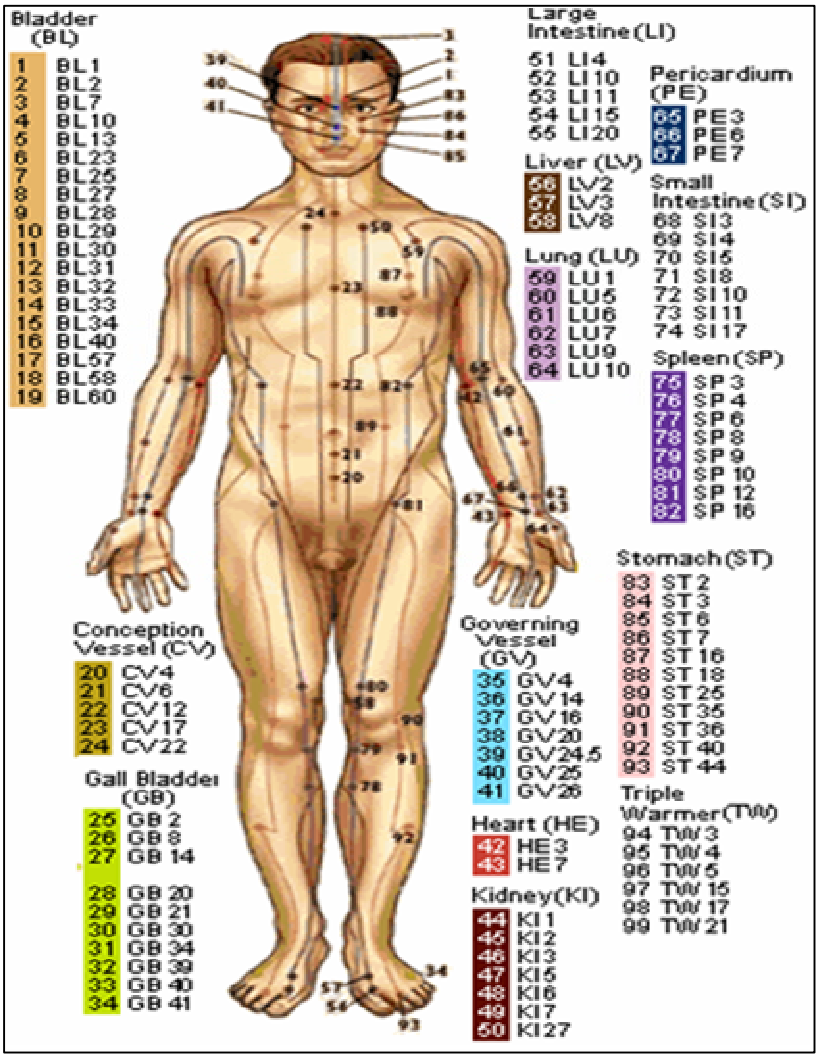


Figure 4-1 Simple body chart for acupuncture points (adapted from http://purenaturalhealing.com/use-acupressure-chart/)

Main meridians are connected to various body organs as well as to each other. They serve as pathways for the flow of 'vital energy' or Qi. Qi (pronounced 'Chee'), or life energy is a key concept in TCM, and it is considered to be the essential element in the healing system. As a consequence, and according to the principle of TCM, imbalances in the flow of energy among the meridians, organs, and five elements (fire, earth, metal, water, and wood) are the cause of disease, pain, and susceptibility to illness (Mayer,,

2000; Sierpina and Frenkel, 2005; Staud, 2007). Furthermore, pain or ill health happens when something occurs to cause meridian energy circulation to be blocked, inserting needles at APs unblock these obstructions, allowing energy to flow again (Manheimer *et al.,* 2010; Suarez-Almazor *et al.,* 2010).

## 4.2 Evidence supporting Efficacy of acupuncture

Acupuncture is one of the non-pharmacological interventions recommended by EULAR for treating KOA (Bjordal *et al.,* 2007). In addition, its use for pain relief is supported by clinical trials, which facilitated its acceptance in pain clinics in most countries (Lundeberg, 2002). Chronic pain, especially musculoskeletal pain syndrome, is the most common reason patients try acupuncture (Kelly, 2009; Vickers *et al.,* 2010). As acupuncture is one of the widely used CAM interventions for pain, a survey released in 2004 by a nationwide study showed that 36% of US adults aged 18 years and over use some form of CAM. Furthermore, more than 20% of the UK population uses CAM each year, and 47% will try CAM at some point in their lifetime (Staud, 2007).

According to Vickers *et al.* (2010), Medline listed over 1100 English language randomised trials of acupuncture in June 2010. However, Staud (2007) reported that Medline databases showed approximately 12,000 articles relating to acupuncture. A large number of systematic reviews on acupuncture for pain have been published, where, for example, the Cochrane Library for 2007 listed 12 Cochrane Collaboration reviews of acupuncture for pain, with over 50 additional non-Cochrane systematic reviews published on this topic (Vickers *et al.,* 2010). Finally, Wang *et al.,* (2013) found 3833 articles during their recent PubMed search of ‘acupuncture clinicaltrials’.

Ezzo *et al.* (2001), in their systemic review, concluded that the evidence suggests that acupuncture may play a role in the treatment of KOA. There is convincing evidence

from RCTs of acupuncture in patients with various diseases, such as low back pain (Weidenhammer *et al.,* 2007; Thomas *et al.,* 2005; Witt *et al.,* 2006a), neck pain (Witt *et al.,* 2006b), shoulder pain (He *et al.,* 2004), fibromyalgia (Martin *et al.,* 2006), postoperative pain (Sun *et al.,* 2008), and headache (Coeytaux *et al.,* 2005; Linde *et al.,* 2009a; Linde *et al.,* 2009b), in addition to many other diseases and complications.

## 4.3 Studies examining the efficacy and effect of acupuncture in the treatment of KOA

There are several reviews that were carried out to determine the efficacy of acupuncture for the treatment KOA. Cochrane reviews have been done by Lee and Ernst (2011) and by Manheimer *et al.* (2010), for numerous conditions including peripheral joint OA of the knee, hip, or hand. Both reviews showed statistically significant benefits of acupuncture in sham-controlled trials. Kwon *et al.* (2006) carried out a systematic review and meta-analysis of acupuncture for peripheral joint OA, where 14 RCTs out of 18 focused on KOA. The authors of the study concluded that acupuncture has a significant effect compared with sham acupuncture, and it seems an option worthy of consideration, particularly for KOA.

Another review was conducted by Selfe and Taylor (2008) to evaluate the effect of both needle and EA on KOA. Ten trials with 1456 participants were analysed, which then provided evidence that acupuncture is an effective treatment for pain and physical function of patients with KOA. A systemic review done by Ezzo *et al.* (2001) to evaluate trials of acupuncture for KOA, and which included 7 trials and 393 subjects, indicated that there was strong evidence for pain reduction using acupuncture compared with the sham treatment. However, there was insufficient evidence for function in such effect.

Overall, reviews on the efficacy of acupuncture have been criticised for significant heterogeneity of acupuncture treatment regimens and inclusion criteria throughout the literature, which makes definitive conclusions difficult. Nevertheless, there was consistency in the literature that acupuncture shows statistically significant benefits for pain and function when compared with sham acupuncture for the treatment of OA (De Luigi, 2012).

Acupuncture for the treatment of KOA has been evaluated by several RCTs with a variety of treatment and sham acupuncture (Table 4-1). Suarez-Almazor *et al.* (2010) conducted a 3-month RCT in patients with KOA to compare the efficacy of traditional acupuncture with sham acupuncture and to examine the effects of acupuncturists' communication styles. Four hundred and fifty-five patients with KOA were randomised into 1 of 3 groups (patients on a waiting list, those with high expectations of success by acupuncturist, or those with neutral expectations). Xi Yan, He Ding, Gb34, Sp6, Sp9, Ear-Knee, and1–2 tender Ashi point proximal to the knee APs were used in traditional acupuncture group.

Primary outcome measures were Joint-Specific Multidimensional Assessment of Pain (J-MAP), WOMAC, and satisfaction scores. Outcome measures were collected at baseline, 4 weeks, 6 weeks (end of treatment), and 3 months. The result of the study showed that traditional acupuncture was not superior to sham acupuncture, and the needling of meridian points was not more effective than the use of sham points. Acupuncturists' communication styles had a small but statistically significant effect on pain reduction and satisfaction.

In a RSBCT carried out to investigate the effect of EA on pain intensity and plasma levels of endorphin and cortisol, Ahsin *et al.* (2009) allocated 84 patients into two groups who received either EA or sham acupuncture. St34, St35, St36, Liv8, Sp10, and

St44 APs were stimulated. Outcome measures were WOMAC and VAS, which were collected on the first day of the treatment session and after ten days of daily treatment. The study suggests that EA is effective for relieving pain, stiffness, and functional disability with an increase in plasma-endorphin and a decrease in plasma cortisol, by comparison with sham acupuncture in patients with primary KOA.

Taechaarpornkul *et al.* (2009) conducted a comparative randomised trial to compare the effectiveness of 6 and 2 APs in the treatment of KOA using EA. Seventy patients were randomised into two groups. The 6-point group received treatment at 6 APs (St35, EX-LE4, St36, Sp9, SP10 and St34) and the 2- point group received treatment at just the 1st pair of points, St35 and EX-LE4. A Thai language version of the WOMAC was a primary outcome, and patients were assessed at baseline, week 5, week 9, and week 13. Acupuncture at both 6 and 2 acupuncture points was associated with a significant improvement; however, there was a non-statistically significant improvement in pain in subjects who received both 2 and 6 APs. Instead, the authors suggest that EA to two local points may be sufficient to treat KOA.

EA and MA were compared with sham acupuncture in a RCT done by Jubb *et al.* (2008) on patients with KOA. Sixty-eight patients were allocated to two groups, to receive acupuncture or sham acupuncture treatment. Li 4, Sp10, Xiyan, Sp9, GB34, St 36, Liv3, Bl40, and Bl57 APs were chosen for the study. WOMAC, VAS, Euro QoL, and plasma β-endorphin were the main outcomes of the study, and they were conducted at baseline, after the 10 sessions of the treatment and at 1 month after treatment. The primary end point was the change in pain after a course of 10 treatments as measured by the WOMAC pain subscale. The result of the study showed that acupuncture is significantly superior to non-penetrating sham acupuncture for patients with KOA. The authors of the study concluded that skin penetration of the needle is required to gain the beneficial effect.

A multicentre RCT has been carried out by Foster *et al.* (2007) to investigate the benefit of adding acupuncture to an exercise and advice program for pain reduction in patients with KOA in older adults. From 37 NHS physiotherapy centres, 352 patients were randomly assigned to three treatment groups. Group 1 received an advice and exercise program, while groups two and three received either true acupuncture or non-penetrating acupuncture on selected acupuncture and trigger points (Sp9, Sp10, St 34, St 35, St36, Xiyan, Gb34, LI4, TH5, Sp6, Liv3, St44, Ki3, Bi60, and Gb41) in addition to the advice and exercise program. WOMAC was the main outcome, and the secondary outcomes were functionality, pain intensity, and unpleasantness of pain at 2 weeks, 6 weeks, 6 months, and 12 months. The results of the study clarified that the addition of acupuncture to a course of advice and exercise for KOA provided no additional improvement in pain scores.

Berman *et al.* (2004) conducted a RCT to determine the efficacy of true acupuncture compared with sham acupuncture or education in patients with KOA. Five hundred and seventy patients were randomly assigned into three groups. Group1 received true acupuncture; group 2 received sham acupuncture; and group 3 received education. Patients received 23 true acupuncture sessions over 26 weeks. Controls received six 2-hour sessions over 12 weeks or 23 sham acupuncture sessions over 26 weeks. Nine APs were stimulated at five local points (Gb34, Sp9, St36, St35, Xiyan point) and 4 distal points (Ub60, Gb39, Sp6, Ki3). WOMAC was the primary outcome and the secondary outcomes were patient global assessment, 6-minute walk distance, and physical health scores of the 36-Item Short-Form Health Survey (SF-36). Assessments were conducted at baseline and 4, 8, 14, and 26 weeks after randomisation. Although 25% of the participants in each of the true and sham acupuncture groups and 43% in the education group were not available for analysis at week 26, the authors concluded that acupuncture appears to provide improvement in function and pain relief as an adjunctive

therapy for KOA when compared with credible sham acupuncture and education control groups.

A RSBCT has been done by Sangdee *et al.* (2002) to compare the efficacy of EA and diclofenac and their combination in the treatment of KOA. One hundred and ninety-three patients with KOA were randomised into 4 groups: placebo, diclofenac, EA, and combined (diclofenac plus EA). VAS, WOMAC, Lequesne's functional index, 50-feet walk time, and the orthopaedist's and patient's opinion of change were the outcomes of the study. Participants were evaluated at baseline and at the end of the study (week 4). The results of the study demonstrated a significant improvement of pain and function with EA compared with the placebo and diclofenac.

A prospective controlled trial comparing acupuncture with no treatment in patients with advanced KOA awaiting TKR has been conducted by Tillu *et al.* (2002). Seventy-five patients were allocated into two groups. Group A received acupuncture on Sp9, Sp10, St34, St36, and Li4 APs at weekly intervals for 6 weeks and group B acted as a control group receiving no treatment. The Hospital for Special Surgery score, time to walk 50 meters, time to climb 20 steps, and degree of pain were assessed. Participants were assessed at baseline and at the end of two months. The result of the study showed that the acupuncture group improved in all parameters, whereas the control group deteriorated.

Similar to LLLT, acupuncture studies have been criticised for several flaws. Although RDBCTs is the gold standard, in studies involving acupuncture, conducting a study in which both the researchers and the patients are unaware of the type of the treatment used would be virtually impossible. Furthermore, there are difficulties in acupuncture study designs because of the variability in recommendation of matching appropriate control group, randomisation, needling techniques, AP specification, number, and

duration of treatment sessions (Ahsin *et al.,* 2009). Foster *et al.* (2007), by the same token, stated that clinical studies of acupuncture have been criticised for small sample sizes, inadequate blinding, and lack of credible sham controls and long-term follow-up. Moreover, it is difficult to know if the positive effect of EA comes from the electrical current or as a result of needle insertion. Furthermore, Qi sensation, which is required for a successful acupuncture treatment, is difficult to apply in animal studies. All acupuncture studies aforementioned suffer one or more of previously discussed flaws.

**Table 4-1 Summary for some studies examined acupuncture as a treatment for KOA**

| **Study** | **Design** | Partici-pants | Intervention and Control | APs | **Endpoint Assessment** | **Baseline (Mean or Median) of primary outcome (VAS)** | **Endpoint mean or Median and/or mean or Median difference between groups; p value** | **Other outcomes** | **Result of the end point assessment (between groups)** |
|---|---|---|---|---|---|---|---|---|---|
| Suarez-Almazor *et al.* (2010) | RCT | 450 | Active group: acupuncture<br><br>Control group : Sham acupuncture | Xi Yan, He Ding, GB34, Sp6, Sp9, Ear-Knee | 3 months | - | - | (J-MAP), WOMAC, and satisfaction scores | Acupuncture was not superior to sham acupuncture |
| Ahsin *et al.* (2009) | Single-blinded, sham-controlled study | 84 | Active group: EA<br>Control group: Sham acupuncture | ST34, ST35, ST36, LIV8, SP10, and ST44) | 10 days | (VAS)<br>No values available in the study | (VAS)<br>No values available in the study | WOMAC | EA is effective for relieving pain |
| Taechaar p-ornkul *et al.* (2009) | Acomparative randomized trial | 70 | Active group: 6 points EA<br><br>Control group: 2 points EA | ST35, EX-LE4, ST36, SP9, SP10 and ST34 | 13 weeks | _ | _ | WOMAC | EA to 2 local points may be sufficient to treat KOA |
| Foster *et al.* (2007) | Multicentre RCT | 352 | Active group I: Exercise and advice<br>Active group II: true acupuncture + exercise and advice<br>Control group: Sham acupuncture + exercise and advice | Sp9, Sp10, St 34, St35, St 36, Xiyan, Gb 34, LI4, TH5, Sp6, Liv3, St 44, Ki3, Bi60, and Gb41 | 12 months | _ | _ | WOMAC, function, pain intensity, and unpleasant ness of pain | No significant difference. |
| _, VAS was not used in the relevant study. | | | | | | | | | |

| **Study** | **Design** | Participants | Intervention/ Control | APs | **Endpoint Assessment** | **Baseline (Mean or Median) of primary outcome (VAS)** | **Endpoint mean or Median and/or mean or Median difference between groups; p value** | **Other outcomes** | **Result of the end point assessment (between groups)** |
|---|---|---|---|---|---|---|---|---|---|
| Berman *et al.* (2004) | RCT | 570 | Active group: acupuncture<br><br>Control group: Sham acupuncture or education | Gb34, Sp9, St36, St35, Xiyan point, Ub60, Gb39, Sp6, Ki3 | 26 weeks | _ | _ | WOMAC, patient global assessment, 6-minute walk distance, (SF-36) | Acupuncture seems to provide improvement in function and pain relief |
| Sangdee *et al*. (2002) | RSBCT | 193 | Control group: Placebo<br>Active group I: diclofenac<br>Active group II: EA<br>Active group III: combined (diclofenac plus EA) | ST35, Medial Xiyan, Liv8 and a trigger point | 4 weeks | Mean:<br>Control group: 6.35<br>Active group I: 6.48<br>Active group II: 6.69<br>Active group III: 5.76 | Mean:<br>Control group: -3.31<br>Active group I: -4.90<br>Active group II: -5.65<br>Active group III: -6.28;<br>$p < 0.05$ | WOMAC, Lequesne functional index, 50-foot walk time | EA was significantly more effective than placebo regarding VAS and Lequesne functional index |
| Tillu *et al.* (2002) | Prospective, non-Randomised CT | 57 | Active group: acupuncture<br><br>Control group: no treatment | Sp9, Sp10, St34, St36, Li4 | 2 months | Median:<br>Active group: 5.1<br>Control group: 5.7 | Median:<br>Active group: 1.0<br>Control group: -0.2;<br>p= 0. 0001 | Hospital for Special Surgery (HSS) score, time to walk 50m, time to climb 20 steps | Acupuncture is an effective treatment for KOA |
| _, VAS was not used in the relevant study. | | | | | | | | | |

# Chapter 5 Patients and Methods

## 5.1 Patient recruitment

The study was carried out at the Physiotherapy Department (PTD) of the Security Forces Hospital (SFH) in Riyadh, Saudi Arabia, from August 2010 to March 2011. Before the study was started, orthopaedic physicians, family medicine and rheumatology clinics were informed about the intention to conduct a study to investigate the efficacy of LLLT on patients with KOA. They were asked to refer any patient suffering with KOA who met the inclusion criteria of the study. Of a total 107 patients who were referred to PTD by their physician for the initial assessment, 25 did not meet the inclusion criteria; 24 refused to participate; and 9 dropped out after they have been randomised, but had not attended the first treatment session including the baseline assessment without clear reasons. Eventually 49 patients completed the study. Figure 5.1 shows the flow of the study.

## 5.2 Inclusion and exclusion criteria of the study

The inclusion criteria for this study were male or female patients who had KOA according to the ACR criteria (Hochberg *et al.,* 1995) (Table 5.1), had an average pain intensity of 3 or more on a 10 cm VAS for the last month before baseline assessment, had an ability to practise all movements included in the evaluation forms, had the ability to read or understand patient information sheets and the ability to sign a consent form. Patients with bilateral KOA had the most painful knee assessed.

**Table 5-1 The ACR criteria for KOA**

| |
|---|
| Knee pain and radiographic osteophytes and at least 1 of the following items: |
| Age > 50 years |
| Morning stiffness ≤ 30 minutes in duration |
| Crepitus on motion |

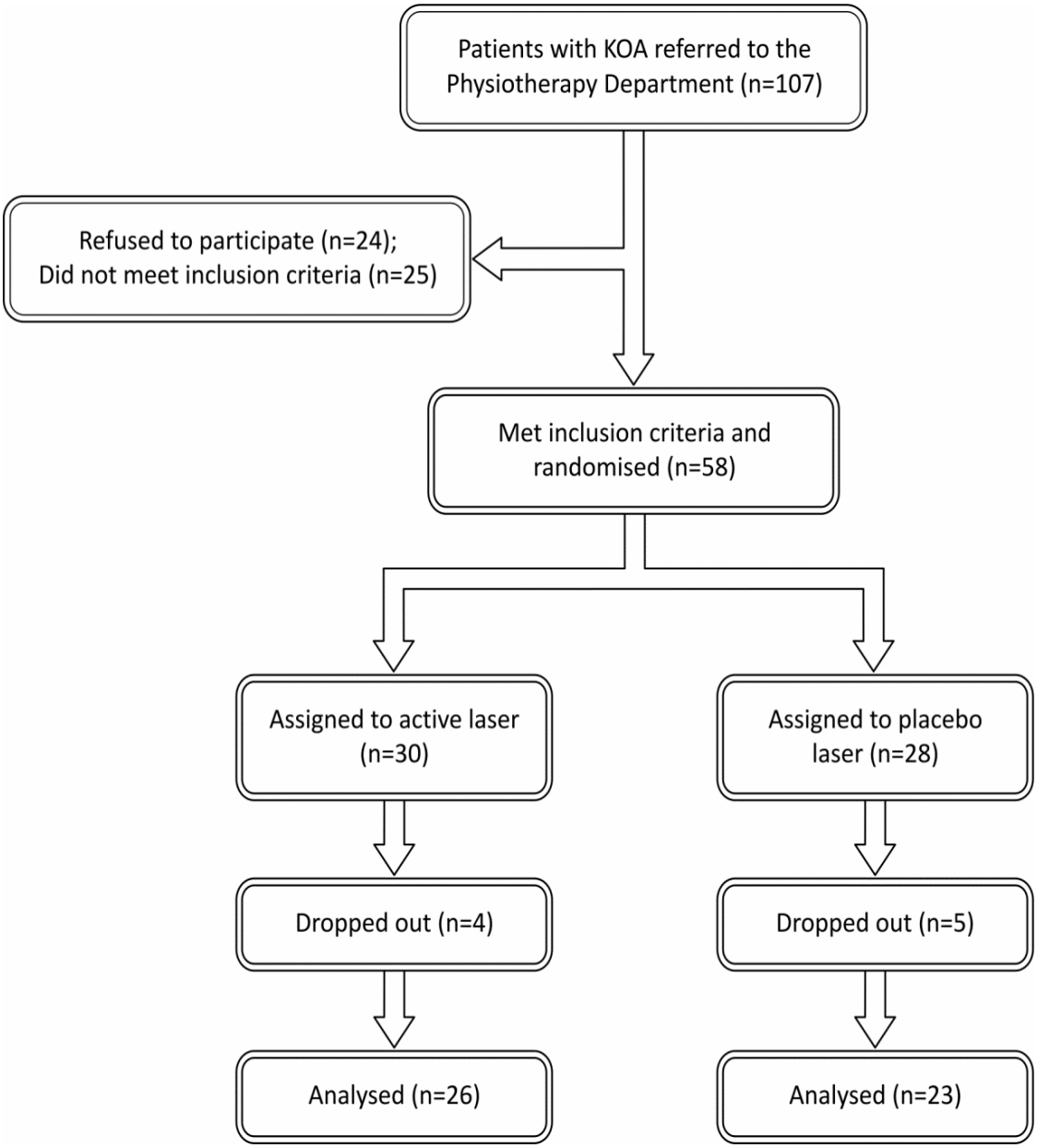


Figure 5-1 Flow of the study

The exclusion criteria included patients with previous knee surgery, serious valgus or varus deformity, any disease which was informed by the treating physician in the referral form and is contraindicated for treating by laser therapy, such as cancer, acute diseases, uncontrolled diabetes mellitus, and untreated hypertension; and finally, patients already on treatment with drugs that could interfere with the intensity of pain for more than six weeks, particularly steroids, were excluded and directed to continue with their medication (Gur *et al.,* 2003; Yurtkuran *et al.,* 2007). Patients were allowed

to take only analgesics as required for severe pain, due to ethical reasons, and to stop any other medication related to their knee pain; their physicians were consulted about this point. A patient information sheet (Appendix II) was read, and written informed consent form (Appendix III) was signed by each participant prior to participation in the study.

## 5.3 Ethical approval and data base registration

The Research Committee of SFH in Riyadh, Saudi Arabia, granted ethical approval for all procedures of this study before starting the clinical trial (Appendix IV). Furthermore, the current study has been registered in the following database:

ISRCTN24010862; Doi 10.1186/ISRCTN24010862.

## 5.4 Study design

It has been reported that the most robust design should be chosen, especially in healthcare, in order to minimise potential bias and maximise generalisability (Eccles *et al.,* 2003). Ohshiro *et al.* (1994) suggested some critical considerations that should be taken into account when conducting a study to investigate the effect of LLLT on pain. They stated that trials should be double-blinded and use an inactive laser as a placebo. Furthermore, Campbell *et al.* (2007) stated that it has been reported that the UK Medical Research Council (MRC) considers that RCTs are the "most scientifically rigorous, unbiased way of comparing alternative healthcare interventions". Moreover, it has been reported that RCTs have been considered as the gold standard method for evaluation of drugs, devices, and procedures (Boutron *et al.,* 2008).

It is important that alternative treatments such as LLLT be subject to rigorous scientific study to establish that they are safe, genuine, and efficacious interventions. Moher *et al.*

(2010) reported that, in healthcare, well designed RCTs provide the most reliable evidence on the efficacy of interventions, unlike poorly designed studies, which are usually associated with biased results.

The current study was performed using a RDBCT design to investigate the efficacy of LLLT on patients with KOA. It is important here to differentiate between the efficacy and effectiveness of intervention. According to Revicki and Frank (1999), the efficacy can be defined as the performance of an intervention under ideal and controlled circumstances, whereas effectiveness refers to its performance under 'real-world' conditions.

Furthermore, the current study was conducted based on the Consolidated Standards of Reporting Trials (CONSORT) statement (Appendix V). The CONSORT statement has been developed by a group of scientists, epidemiologists and editors in order to improve the quality of reporting of RCTs. It was first published by Begg *et al.* (1996) and further meetings of the group led to the publication of the revised CONSORT statement 2001. Several versions of CONSORT have been updated after that (Boutron *et al.,* 2008; Moher *et al.,* 2010; Nelson and Mathiowetz, 2004).

### 5.4.1 Randomisation

Adequate randomisation reduces selection bias at study entry and is the crucial component of high-quality RCT studies (Moher *et al.,* 2010). In the current study, 58 patients were randomly assigned to one of the two study groups, the active laser group (n = 30) or the placebo laser group (n = 28), using software-generated randomised numbers; the randomisation depended on random blocks of 10 (Dallal, 2010). Appendix VI shows the randomisation table.

### 5.4.2 Blinding

Blinding is an important component to the study quality. To ensure that the current study was conducted in a double-blind fashion, both the investigator and the patient were unaware of whether placebo or active treatment were utilised, and only the research assistant had the identifying code to determine which treatment was given (Figure 5.2).

Figure 5-2 Blinding technique, only the research assistant determines the code of the treatment.

Moreover, the laser device was placed behind both the patient and the investigator, and it was covered by a hard cover paper. The same laser device was used for both groups. The placebo emitter is identical in appearance to the active emitter, but it is inactive (both produce red light); no heat, sound, or vibration is detectable from either the active or the placebo laser.

## 5.5 Measurement tools

Prior to the current study being conducted, the expectations were that most participants might be elderly patients who had low levels of education, so, valid, reliable, and simple measurement tools have been used to meet older patient's capabilities. According to Herr and Garand (2001), it has been reported that patients' self-report is the most accurate, reliable, and well-established tool for measuring the existence of pain and its intensity, furthermore, a few adaptations could be applied when measuring pain with standard scales to meet the older person's capabilities. In the current study, the average age of participants was 54 years, their mother language was Arabic language, and 61% of them were uneducated. For the previously mentioned reasons, an adapted Arabic language VAS was used in the current study (Appendix VII). Furthermore, the current study was conducted in Saudi Arabia, and it was applied to Saudi patients, therefore, the SKFS was used taking into account cultural characteristics (Appendix VIII).

The outcome measures were the level of pain, QoL, ROM, KC, and patient satisfaction. The tools used to assess the outcomes were the adapted VAS (in Arabic language), the SKFS (total) (Appendix VIII), goniometry, a tape measure, and the percentage assessment of patient satisfaction (%), respectively; more details about these measurement tools are presented in sections 5.5.1 to 5.5.5. In the current study, all patients were tested by the same assessor, and they were assessed at baseline, at the 5th session of treatment, at the last session of treatment and at 6 weeks and 6 months after the last treatment session.

### 5.5.1 VAS

The primary outcome of the current study was the change in the VAS score for pain during movement. The VAS is the most frequently used measure of pain in clinical and

research settings, especially where changes in symptoms are to be recorded (Ahsin *et al.,* 2009; Katz and Melzack, 1999). The VAS has been shown to be a reliable and valid measure of pain, and it only gives information about the intensity of the pain (Katz and Melzack, 1999; Pritchard, 2010). However, the VAS has been criticised because of its unidimensional measures, which have scaling difficulties and possible lack of sensitivity. In addition, the information that is provided by these scales is limited to only the intensity of the pain and it cannot be used to assess variations in the type of pain, such as burning, piercing etc. (Martinez *et al.,* 2011).

Furthermore, small changes in the VAS may have statistical significance, without clinical meaning (Lee *et al.,* 2003). It has been reported that failure to use the VAS correctly has been attributed to a variety of factors including educational level. In the current study, adapted Arabic language VAS was used, which consists of a 10 cm line anchored at each end. The right-hand anchor reads 'no pain' and left-hand anchor reads, 'worst possible pain'. The patient is asked to mark on this line how much pain is being experienced. The score is read in centimetres, from 0 –10 cm.

### 5.5.2 SKFS

The changes in the SKFS scores for pain, stiffness, and physical function and social and emotional functions were used. The SKFS contains activities especially related to Arabic and Muslim societies, which are not present in other commonly used indices, such as WOMAC index, which is widely and commonly used in similar studies. People in Saudi Arabia and many other Arabic and Islamic countries bend their knees extensively during several activities, such as during prayer (minimum five times daily) (Figure 5.3), sitting on the ground during meals, at social gatherings (Figure 5.4) and

also for the toilet (Arabic squat style toilet) (Figure 5.5). These activities are included as items in the SKFS.

Figure 5-3 Prayer positions (adapted from, http://www.exoticindiaart.com/article/islam/)

SKFS is a reliable and valid scale, which was developed by Al-Sobayel (1997), in her study (Construction and Validation of the Saudi Knee Function Scale). Her study was submitted to the School of Rehabilitation Therapy, Queen's University, Canada, in August 1997. The reason for her study was that studies of disability evaluation and outcome measurement of the KOA in Saudi Arabia were not available. Therefore, her study has contributed to filling this gap and providing information on the effect of this disease on Saudi people.

Figure 5-4 Sitting on the ground during meals and at social gatherings

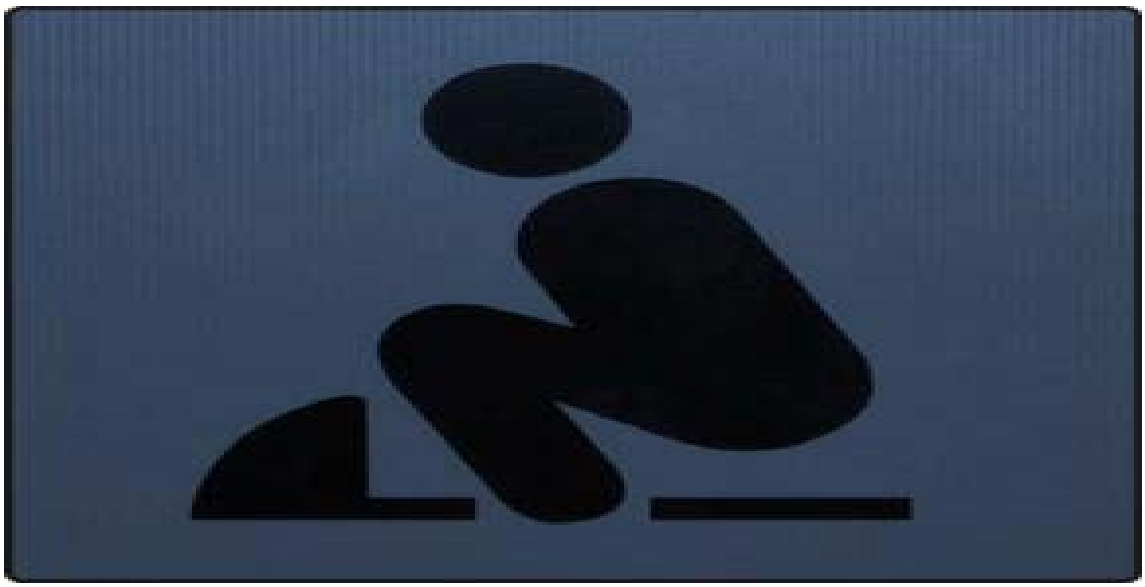

Figure 5-5 Arabic squat style toilet (http://johnnyvagabond.com/featured/how-to-use-a-squat-toilet-in-5-easy-steps/)

The SKFS index is an Arabic language validated, multidimensional, and self-administrated questionnaire, used to assess pain, stiffness, and physical function, social and emotional activities for KOA (Appendix VIII). SKFS consists of a 5-dimensional measure of pain, stiffness, physical function, social function, and emotional function. The pain subscale includes 8 questions about pain, the stiffness subscale includes two questions about stiffness, the physical function subscale (PF subscale) includes 12 questions about the degree of difficulty when practising specific activities, the social function subscale includes three questions about social activities, and finally, the emotional function subscale includes three questions about feelings because of knee. For more details see Appendix (VIII).

Each of the 28 questions in the SKFS is graded on a 5-point Likert scale ranging from 0 (no symptoms) to 4 (maximum symptoms). In the SKFS, the maximum total score possible is (112), which is calculated by the addition of the five sections (pain = 32 maximum score; stiffness = 8 maximum score; physical function = 48 maximum score; social function = 12 maximum score; and emotional function = 12 maximum score) of this scale, indicating the worst suffering possible, and the minimum score is zero (0), indicating the absence of suffering.

### 5.5.3 Goniometry

Measuring joint mobility could be used as a tool to assess disease severity and to document recovery after various interventions (Cleffken *et al.,* 2007; Naylor, 2011). Even though a variety of instruments for measuring joint mobility have been developed, ranging from simple visual estimation to high-speed cinematography, the universal goniometer (full-circle manual goniometer) is still a crucial instrument that is used extensively for measuring knee ROM in orthopaedic and rehabilitation practice (Bennett *et al.,* 2009; Miner *et al.,* 2003; Naylor *et al.,* 2011; Santos *et al.,* 2012). It has been reported by Gogia *et al.* (1987) that goniometric measurements of the knee joint are both reliable and valid. However, Naylor *et al.* (2011) stated that the validity and reliability of goniometers are critical to note. Whereas, Watkins *et al.* (1991) reported that goniometric measurements for passive ROM are highly reliable when taken by the same therapist. Standard plastic two-arm 360° goniometer, with 30-cm movable arms, and a scale in 1° increments was used in the present study. The specific procedure adopted in this study is carefully described in section 5.8.1.5, with a description of the tools and practical steps.

### 5.5.4 Tape measure

One of the common symptoms associated with patients with OA is joint effusion (Cho *et al.,* 2011; Majima *et al.,* 2012). Joint effusion is an excessive accumulation of fluid within the joint capsule (Sturgill *et al.,* 2009). An ordinal tape measure is the frequently used instrument in the assessment of effusion of the knee joint, in order to monitor and guide rehabilitation (Jakobsen *et al.,* 2010). The ordinal tape measure is simple, cheap, fast, and easy to apply, and it is a readily available instrument to measure joint circumference (Nicholas *et al.,* 1976; Sturgill *et al.,* 2009). Furthermore, the reliability

of this instrument was reported to be excellent (Holm *et al.,* 2010). In the current study, a non-adhesive ordinal tape measure of total length 152 centimetres was used to measure KC. An illustration of the tape used and the specific practical procedure is presented in Sectioin 5.8.1.6.

### 5.5.5 Patient satisfaction (%)

There are many outcome instruments available and used in clinical trials to assess how a patient feels. Patient-reported outcome, QoL, health status, psychometric, and patient satisfaction are examples of these instruments (Scoggins and Patrick, 2009). Patient satisfaction in the current study focuses on the patient's satisfaction about the benefits they have had from treatment and not about the quality and type of health care services received. For the current study, the patient satisfaction assessment procedure is presented in detail on page 98, Section 5.8.1.7.

## 5.6 Laser device and its parameters

The laser device used in this study was a gallium-aluminium-arsenide (GaAlAs) (Endolaser 476, Enraf Nonius, Botterdam, Netherlands) with a single 30 mW diode probe, infrared-producing laser with a wavelength of 830 nm and an irradiation area 0.28 $cm^2$ (Figure 5.6). To ensure that it was working properly, the power of the probe was checked prior to the first treatment session of the day, using a beam tester incorporated in the equipment itself. For the same reason, the laser device was checked by a specialist from the hospital maintenance department before treatment commenced.


Figure 5-6 Laser device

It is well-known that lasers with wavelengths ranging from 600 to 700 nm are used for treating superficial tissues, while wavelengths between 780 and 950 nm are used for deeper tissues (Chung *et al.,* 2012; Hamblin and Demidova, 2006). Furthermore, laser beam from the diode laser, particularly the (GaAlAs, 830nm) has the highest penetration rate (Houreld, 2006), as in the red and NIR spectral region, haemoglobin, as a photo-acceptor, does not absorb in this region, and light can penetrate deep into living tissue. Even more, it has been reported that the GaAlAs laser (830 nm) is effective in accelerating the healing process of bone injuries; previous mentioned features together support the decision that this type of laser is one of the best to be used in the current study.

## 5.7 Acupuncture points

Unlike previous laser acupuncture studies for treating KOA that used only one AP, the current study used five APs on and around the knee joint that were irradiated by LLLT. The five APs used in the current study were selected by the researcher because they are frequently used local points for treating KOA by acupuncturists in clinical and research

settings (Ahsin *et al.,* 2009; Berman *et al.,* 2004; Foster *et al.,* 2007; Taechaarpornkul *et al.,* 2009) (Figure 5.7), and because the intention was to determine the efficacy of LLLT when applied to local APs around the affected knee. Furthermore, using more than one AP makes the current study more comparable to clinical trials involving conventional acupuncture. Table 5.2 shows the location, indication, and action in TCM for each of the five APs (Berman *et al.,* 1999; Hecker *et al.,* 2008).

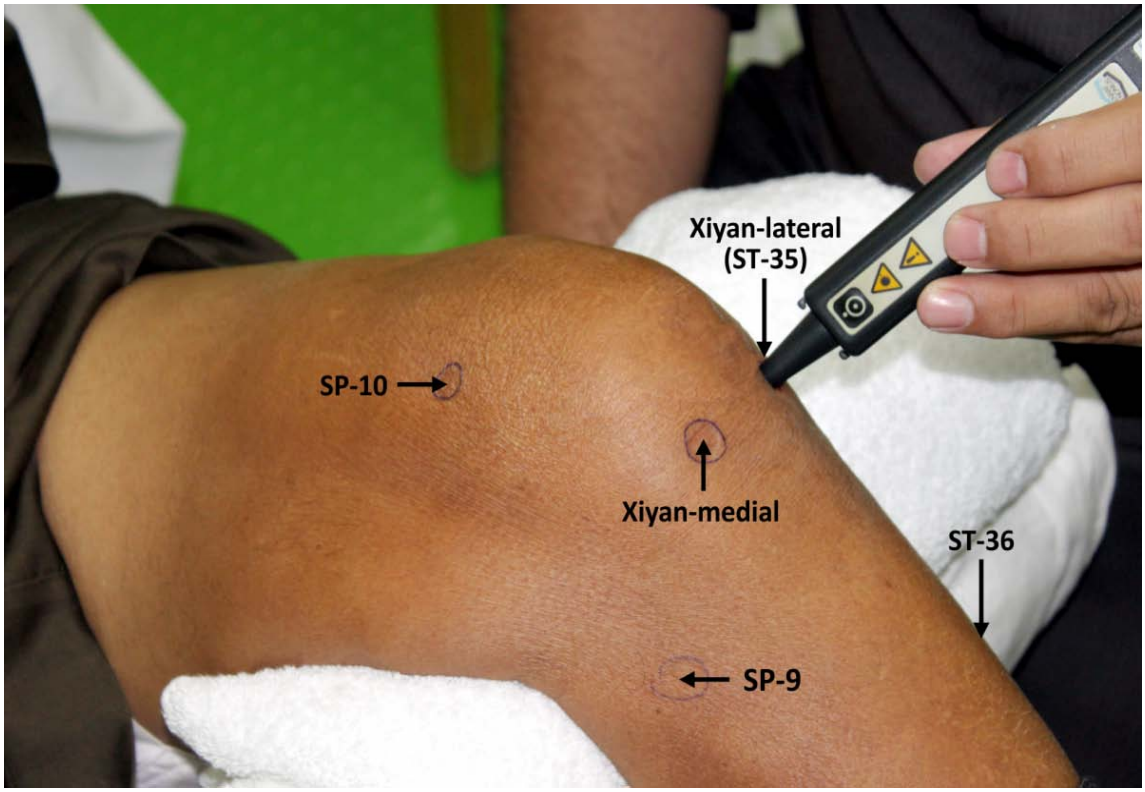


Figure 5-7 Five acupuncture points used in the study

**Table 5-2 The APs which were irradiated in the study***

| APs | Location | Indication | Action in TCM |
|---|---|---|---|
| (ST-35) Xiyan-Lateral | With the knee slightly flexed, below the patella and lateral to the patellar tendon. | Pain, numbness, and motor impairment of the knee joint. | Removes obstruction from the channel, reduces swelling and pain, and expels wind, dampness, and cold. |
| (Ex-LE-4) Xiyan-Medial | With the knee slightly flexed, below the patella and medial to the patellar tendon. | Knee pain, weakness of lower extremities. | Dispels wind-dampness, reduces swelling, and alleviates pain. |
| ST-36 | With the knee slightly flexed, roughly at the level of the lower border of the tibial tuberosity. | Gastric pain, aching of the knee joint and leg, and emaciation due to general deficiency. | Strengthens spleen and stomach, regulates the circulation of the blood, removes dampness, dispels exterior pathogenic cold, regulates the intestine, and stabilizes the mind and emotions. |
| SP-9 | On the inferior border of the medial condyle of the tibia, in the depression between the posterior border of the tibia and the gastrocnemiumuscle. | Abdominal pain and distension, diarrhoea, oedema, jaundice, dysuria, and pain in the knee. | The most important point for removing dampness and moisture; regulates the urinary tract and remove obstruction from the channel. |
| SP-10 | With the knee flexed, when placing the palm onto the patella with the thumb slightly spread, it lies in the front of the tip of the thumb. | An important immune modulating point. | Regulates blood, cools blood, circulates blood, removes stagnation, tonifies blood, and regulates menstruation. |
| * (Berman *et al.,* 1999 ; Hecker *et al.,* 2008) | | | |

## 5.8 Procedures

Once the patient arrived at the PTD with a physician referral, the initial information was taken (Screening visit), such as the knee involved, duration of symptoms, pain intensity, previous treatment, and other medical factors, to ensure that the patient met the inclusion criteria of the study. Then, if the participant met the inclusion criteria, he or she would be informed that there was a study being done to evaluate the efficacy of LLLT in the treatment of KOA. From the beginning, the participants were provided with details about the procedures and the purpose of the study, such as participation procedures, confidentiality safeguards, attendance requirements, assessment, treatment procedures, and any risk from the treatment (Appendix II, patient information sheet). All participants were unaware of the hypothesis of the study, and were unaware which type of treatment they would receive, to minimise bias from the participants (double-blinded). Patients were then given enough time to read the patient information sheet and were allowed to ask any related questions. Each participant was then required to sign the informed consent form prior to participation in the study (Appendix III, consent form). After that, participating patients were given an appointment to start the study, whereas excluded patients were given an appointment with another therapist to be treated according to the PTD treatment strategy for these cases. When the participant came to his or her appointment at the PTD, baseline data were collected immediately prior to the first treatment session.

### 5.8.1 Data collection

#### 5.8.1.1 Demographic information

Demographic information was taken, such as the patient's name, age, sex, marital status, level of education and occupation, knee involved, duration of symptoms,

previous treatment, and other medical factors. Demographic information was recorded on special forms previously prepared for this reason (Appendix IX).

#### 5.8.1.2 Weight, height, and BMI

Height and weight, were measured using a digital scale (Health-O-meter 500KL Digital Medical Scale with Height Rod, capacity of 500 lbs or 227 Kg) (Figure 5.8). Each participant was instructed to remove shoes and any jacket or other heavy garment and then stand on the scale, and then readings were recorded pro-forma. Height and weight were measured, and BMI was calculated at the baseline only.


Figure 5-8 Health-O-meter 500KL Digital Medical Scale with Height Rod.

#### 5.8.1.3 Pain intensity

VAS was the main outcome tool for the current study. Prior to the first treatment session, the modified 10 cm VAS was used to assess the intensity of the pain, while the evaluation was conducted at all of the relevant study points, the last one at 6 months. In the current study, despite the participants having a variety of educational backgrounds, ranging from illiterate to higher education, the same level of illustration (same words and same information) was provided by the investigator for each participant to instruct them in how to use the VAS in order to prevent any bias.

The participant was asked to anchor a short vertical line on the horizontal line representing how much pain was being experienced. The consolidated question for all participants was as follows: identify how your pain is felt during the past period by marking a short vertical line on the horizontal line. The more you move to the left-hand side of the scale, the worse your pain is, and the closer you are to the right-hand side of the scale, the less pain you are experiencing (mirror image of the western system). The score is read in centimetres (cm), starting from the right (no pain) to the left (worst possible pain). Appendix X shows the VAS scores of each participant throughout the study.

#### 5.8.1.4 Quality of life (QoL)

All participants were asked to complete SKFS on their level of pain, stiffness, physical disability, and social and emotional problems associated with the affected knee. Similar to the VAS assessment, the QoL evaluation was conducted at the baseline, at the 5th treatment session, at the last treatment session, at 6 weeks and 6 months after the last treatment session.

Despite the SKFS being a self-administrated questionnaire, in the current study, because 61% of the participants were uneducated and some of them were illiterate and could not read or write, the SKFS forms were filled out by the investigator himself according to each patient's assessment at the time of the consultation to reduce and keep any bias to a minimum. The 28 questions of the SKFS were read for each participant by the investigator, and then circles were marked around 0, 1, 2, 3, or 4 according to each patient's assessment and request. Appendices XI and XII show the SKFS (total) and the SKFS subscales scores of each participant throughout the study.

#### 5.8.1.5 ROM

The degree of active knee angle flexion was assessed using a standard goniometer. Greater trochanter and the lateral epicondyle of the femur and lateral malleolus of the fibula were used as landmarks in order to maintain accurate alignment of goniometer at each of the measurements. To measure the ROM, each participant was asked to lie in the supine position with the affected knee joint clear of clothes. Then, the centre of goniometer body was placed on the lateral epicondyle of the participant's femur, and the stationary arm of the goniometer was aligned with the midline of the femur, using the greater trochanter for reference. After that, the participant was asked to bend her/his knee as much as they could without pain; while the moving arm of the goniometer was aligned with the lateral malleolus of the participant. Three measurements were taken each time, and the mean of the three measurements was recorded. Finally, the reading was recorded on a pro-forma. This process was conducted at the baseline, at the 5th and the 9th (last) session, at 6 weeks and at 6 months after the last treatment session.

#### 5.8.1.6 Knee Circumference (KC)

KC was measured using a standard tape measure at the middle part of the patella of the affected knee. The medial malleolus of the fibula was used as the reference mark; the same distance from the medial malleolus to the middle part of the patella was marked in order to fix the measurement point of the KC assessment at each assessment. The measurement was performed directly on the skin from a supine position for each participant, and the circumferential measurements were recorded on a pro-forma. Similar to the ROM assessment, measurements were taken three times, and the mean of the three measurements was recorded. This measurement was conducted at the baseline, 5th session, last session, and at 6 weeks and 6 months after the last treatment session.

#### 5.8.1.7 Satisfaction

The participants were asked to rate their satisfaction with the intervention received, to see if they felt they had gained any benefit. The assessment was performed using a verbal numeric scale (0% indicates no improvement or benefit, 100% indicates full improvement or benefit; in blocks of 5%). The consolidated question for all participants was "Are you satisfied with your treatment? Please, give a percentage ranging from 0% (no benefit) to 100% (full benefit)". The evaluation was conducted at the 5th session, the last treatment session, and at 6 weeks and 6 months after the last treatment session.

### 5.8.2 Treatment procedure

A series of 9 treatment sessions was given to each patient over 3 weeks, 3 times a week.

#### 5.8.2.1 Laser intervention

To ensure safety, confidentiality, and privacy of participants and others, a separate quiet room was used for treatment and data collection procedures. Patients were placed on a bed in a comfortable and safe sitting position, using a single electric adjustable bed, with the affected knee slightly flexed and supported by a rolled towel (Figure 5.7).

The five APs were determined by the investigator, who was trained to locate these points on healthy patients and volunteers prior to the current study being conducted, using anatomical landmarks (Table 5.2). Furthermore, to ensure that the same points were treated on each occasion, the same supported rolled towel was used each time, and all patients have been advised to keep a circle line that was outlined by the investigator around each AP at the first treatment session as much as possible (see Figure 5.7).

Because the current study was conducted in a double-blind fashion, only the research assistant had the identifying code to determine which treatment was given. The laser device was operated and programmed by the research assistant prior to each single

treatment session depending on the type of intervention: active or placebo treatment. Furthermore, the laser device was placed behind the investigator who performed the treatment, thus ensuring the blinding process. The same tools, materials and patient position were used each time in order to assure consistency in the delivery of the intervention.

The investigator, the research assistant, and the patient wore protective goggles to guard their eyes from active laser radiation. On the affected knee, the laser probe was sequentially and perpendicularly placed at the five APs, which are the commonly used points for treating KOA (Figure 5.7 and Table 5.2). The laser probe was fully contacted with the skin with a firm pressure to maximise the irradiation or power density on the tissue surfaces (Figure 5.7). For all patients of both groups, the five APs were irradiated in the same order (Xiyan-Medial, Xiyan- lateral, ST36, SP10 and then SP9).

In the active laser group, a continuous laser beam irradiated each point for 40s with a dose of 1.2 J/point, 6 joules per session for each patient; this dose is somewhat lower than that recommended by WALT for Laser Therapy for a 830 nm laser (WALT, 2010). The energy density was 4 J/cm$^2$. According to Litscher and Opitz (2012), the Australian Medical Acupuncture College recently stated, 'the optimal energy density for laser acupuncture and bio-stimulation, based on current clinical experience, is 4 J/cm$^2$'. Furthermore, Huang *et al.* (2009) indicated that LLLT delivered at low doses may produce better results when compared to the same wavelength delivered in high doses. Additionally, previous studies showed that LLLT at energy densities up to 4 J/cm$^2$ had stimulating effects. Moreover, a study done by Jia and Guo (2004), who compared doses ranging from 1 to 6 J/cm$^2$, found a greater proliferation of chondrocytes at doses of 4–6 J/cm$^2$. According to Azevedo *et al.* (2006), energy density of 2–4 J/cm$^2$ has shown to be most effective at improving cell growth. These reasons, together with the

previously discussed parameters, have been used in the current study in order to stimulate APs.

The same procedures were applied to patients in the placebo group, but this time the device was inactivated, only producing the visible red light. Note that the laser probe contains start/stop icon, where the start icon was pressed by the investigator for starting the treatment for 40 s, using a stop watch, the icon is pressed again to stop the treatment for the first AP, and then this process was applied again with the remaining APs, sequentially. The procedure allows the investigator to provide the treatment with no need to look at the device's screens, which ensures that the treatment was done in a blinded fashion. The stop watch used in the current study was sufficiently accurate in determining the length of treatment, because it was compatible with the laser machine timer, which was tested prior the trial being conducted.

#### 5.8.2.2 Strengthening exercise

According to Pendleton *et al.* (2000), these exercises directed towards increasing the strength of the quadriceps and/or preserving the normal mobility of the knee should be strongly recommended. In the current study, in both groups, patients were given an exercise therapy programme, with exercises to perform after each session, and advised to repeat them at home at least 5 times daily. The exercise program should be tailored to the individual patient capacity, taking into account factors such as age and co-morbidity. SLR exercise was chosen as the isometric quadriceps exercise. This exercise is easy to perform even for elderly patients (Figure 5.9).

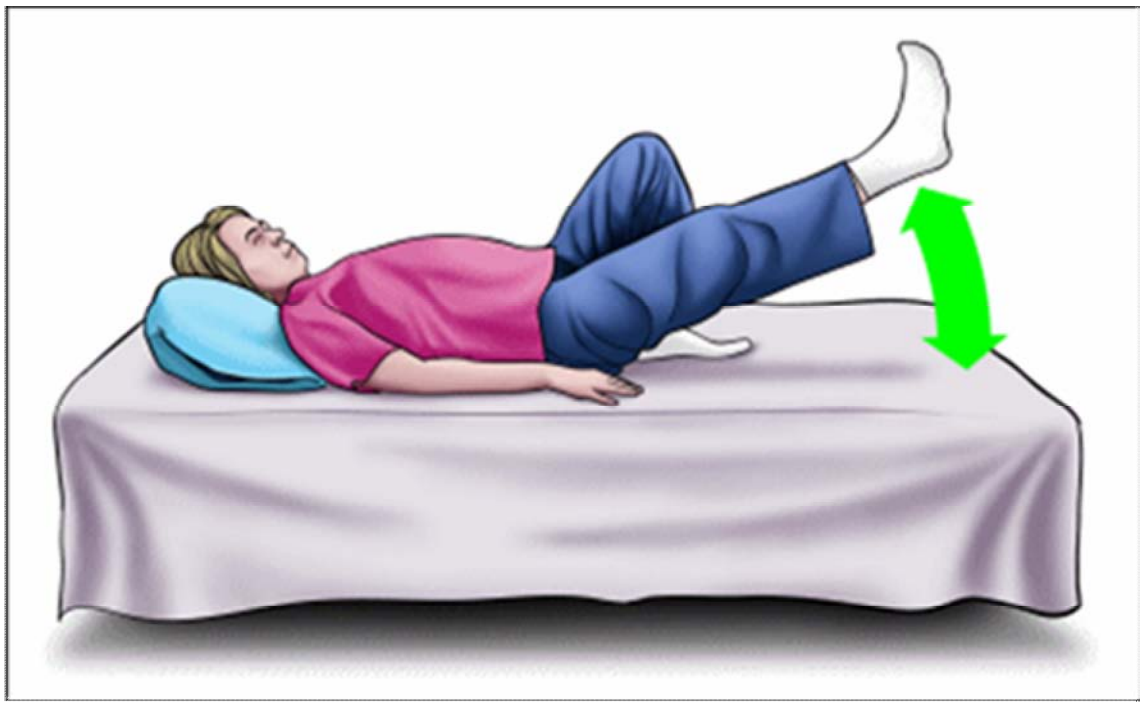

Figure 5-9 Straight Leg Raises exercise (SLR), one leg is bent, and the other leg is kept as straight as possible and tightens muscles on the anterior aspect of thigh. Leg lifts straight 10 inches off the bed and is held for 10 s, and then it is lowered (Adapted from http://www.cpmc.org/learning/documents/rg-tkr-prepare.html)

#### 5.8.2.3 Home instructions and advice

Patients in both groups were given advice and instructions regarding their problems and how they should be dealing and coping with KOA. Obese or overweight patients were advised to lose weight, whereas others were advised to maintain their weight within a normal range, and they were advised to eat healthy food. Patients were advised not to bend their knees excessively, to wear comfortable shoes, to use aids or support such as a walking stick if necessary, and to avoid heavy activities such as lifting heavy objects while climbing stairs. Additionally, all patients were advised to perform their exercise gently, slowly, and ideally as often as possible.

## 5.9 Statistical analysis

It has been reported that in data analysis, the choice between parametric and non-parametric procedures is not easy. However, the parametric test is a more sensitive tool for statistical analysis, and there are certain requirements which have to be fulfilled. For

instance, data should be normally distributed; data must be of an interval/ratio level of measurement and sample size should be large enough. In the event that previous requirements cannot be fulfilled in a study or if there is any doubt, then a non-parametric test should be sought (Hicks 2004; Sim and Wright, 2000).

In the current study, if the data have fulfilled the parametric test requirements, it will be presented as mean (standard deviation (SD)), mean difference, and the confidence interval of the mean difference (95% CI). Otherwise, if the data have failed to fulfil the parametric test requirements and the non-parametric tests have been used, the data will be presented as median, interquartile range (IQR), and median difference (Olsen, 2003; WALT, 2006). In the current study, data was analysed using the SPSS (Statistical Package for the Social Sciences, Chicago) version 17.0 for Windows and Microsoft Excel 2010. The treatment allocation code was broken (un-blinded) after all the participants had completed all assessments.

### 5.9.1 Sample size

To estimate the sample size to be collected, a power analysis was done. From previous studies, the clinical difference was set to be 3.0 points on VAS (Lee *et al.,* 2003), and SD was taken as 3.49, based on a previous study on laser acupuncture in KOA (Yurtkuran *et al.,* 2007), with the Type I error rate being 0.05 and the power as 0.8. The estimation sample-size calculation indicated that at least 21 participants in each group were required (Armitage *et al.,* 2001). Therefore, the number of participants in the current study, set at 26 and 23, respectively, in each group, is sufficient.

## 5.9.2 Test for normality

Prior to the within-group and between-groups analyses, the normality of the data was assessed using the Shapiro-Wilk test. The Shapiro-Wilk test has been recommended for use with the sample-size less than 50 (Razali and Wah, 2011; Ahad *et al.,* 2011). This test gives a value between 0 and 1; the closer the test statistic is to 1, the greater the likelihood that the distribution of the data is normal. In the case of $p > 0.05$, then the data can be assumed to be normally distributed. No normality test needs to be applied for nominal data (gender, affected knee, level of education, occupation) and ordinal data (SKFS (total), SKFS (subscales), and patient satisfaction), because this type of data must be analysed by non-parametric tests.

## 5.9.3 Test for correlation

In order to find out if there was a correlation between some variables, the Pearson correlation test has been used for numeric data, whereas Spearman's rho correlation test was used for non-numeric data. The strength of the correlation was based upon the table taken from statistical correlation - http://www.explorable.com/statistical-correlation (Table 5.3). However, p-value should be $< 0.05$ in all cases.

**Table 5-3 Strength of correlation table**

| Value of r. | Strength of relationship |
|---|---|
| -1.0 to -0.5 or 1.0 to 0.5 | Strong |
| -0.5 to -0.3 or 0.3 to 0.5 | Moderate |
| -0.3 to -0.1 or 0.1 to 0.3 | Weak |
| -0.1 to 0.1 | None or very weak |

### 5.9.4 Baseline data analysis

It has been reported that definitive conclusions of the study regarding the differences in response to the treatment cannot be drawn unless demographic data and initial baseline measures are comparable between the two groups of a research study (Thomas and Nelson 1990; Portney and Watkins, 2000).

In the current study, data were compared between groups using different statistical tests to determine if there were any statistically significant differences in the baseline measures between the two groups. The independent samples t-test was applied for data that fulfilled the parametric test requirements, while the Mann-Whitney U test and Chi-square test were applied for non-normal distributed, ordinal, and nominal data.

Baseline characteristics, such as gender, affected knee, and level of education, were analysed using Chi-square test, and age, height, weight, BMI, VAS, and KC were analysed using the independent samples t-test; while, SKFS, ROM and patient satisfaction were analysed using the Mann-Whitney U test. In this stage, the differences between both groups of the study should be non-significant. Non-significance was expressed by a p-value greater than 0.05 ($p > 0.05$).

### 5.9.5 Within-group analysis

Within-group analyses were conducted to assess changes in the outcome variables within each group of the study separately. Where data fulfilled the parametric test requirements, the paired Student t-test was applied; otherwise the Wilcoxon signed-rank test was used.

SKFS (total), SKFS subscales (pain, stiffness, PF, SF, and EF), ROM, and patient satisfaction were analysed using the Wilcoxon signed-rank test. However VAS and KC

were analysed using the paired Student t-test. The significance of the tests was expressed by a p-value less than 0.05 ($p < 0.05$).

### 5.9.6 Between-groups analysis

Between-groups analyses were conducted to assess differences in the outcome variables between the active laser group and the placebo laser group. Where data fulfilled the parametric requirements, the independent sample t-test was applied; otherwise, the Mann-Whitney U test and Chi-square test were applied.

SKFS (total), SKFS (subtotals), ROM, and patient satisfaction were analysed using the Mann-Whitney U test. Nevertheless, VAS and KC were analysed using the independent samples t-test. The significance of the tests was expressed by a p-value less than 0.05 ($p < 0.05$).

### 5.9.7 Subgroup analyses

In the current study, analyses were undertaken to investigate if a response to the treatment is different across particular groups of patients. The interaction effect between subgroup and treatment was tested using Univariate Analysis of Variance (UAV) (see Section 6.5.6).

## 5.10 Research operator

The operator of the current study completed his Bachelor degree in Rehabilitation and Physiotherapy from King Saud University in Riyadh, Saudi Arabia; and earned a Master's degree in Physiotherapy from the University of Manchester, UK. He has 14 years clinical experience in rehabilitation and physiotherapy. Prior to conducting the

current study, the research operator had had training and attended many courses in laser and acupuncture therapy. The researcher had the opportunity to learn and practice LLLT by attending two LLLT courses (one in London, UK, the other in Riyadh Saudi Arabia organized by THOR (http://www.thorlaser.com/courses/) (Appendix XVII). The researcher also had the opportunity to learn and practice the location and identification of the APs related to this study at a private clinic for acupuncture treatment at Riyadh, Saudi Arabia. During his Master's and PhD study, the research operator had attended courses in research methodology and medical statistics.

# Chapter 6 Results

## 6.1 Introduction

A total of 107 patients were referred to the PTD for the initial assessment, 25 did not meet the inclusion criteria; 24 refused to participate; and subsequently 9 dropped out (4 from active group and 5 from control group) prior to the start of the first treatment session without any reasons given and were completely excluded from the study without affecting the minimum required number of subjects per group as per the power of study (refer to Section 5.9.1). Hence, a total of 49 patients who met the inclusion criteria of the study were included and completed the treatment phase of 9 sessions for 3 weeks, and the same number completed the follow-up periods. Figure 5-1 displays the participants' flow through the study. All data sought were obtained, and there were no missing data points.

Raw data are presented in Tables 1 and 2, which are presented in Appendix XIII. Tables in Appendix XII indicate the gender (F/M) of each subject in both groups of the study, along with the age, height, weight, BMI, affected knee, level of education, and occupation. Tables in Appendices XIV, XV, and XVI indicate all outcome measurement scores of ROM, KC, and patient satisfaction, respectively, for each subject in the both groups of the study, from baseline to all follow-up periods.

## 6.2 Baseline data

Of the 49 participants in the study, 26 were randomly allocated into the active laser group (G1), and 23 into the placebo laser group (G2). Thirty-one of them were women (63%) and 18 were men (37%), with an average age of 54.1 and SD 10.2 years. Demographic and baseline data from all 49 participants are presented in Table 6.1. Age, height, weight, BMI, affected knee, level of education, VAS, SKFS, ROM, and KC of both groups were compared to investigate if the participants in each group originated from the same study population. There were no statistical differences in

demographic data and baseline measurements observed between groups. Table 6.2 shows tests for distribution for numeric data.

**Table 6-1 Demographic data and baseline measurements of both groups**

| Characteristics | G1 (n=26) | G2 (n=23) | p-value |
|---|---|---|---|
| Gender | | | |
| Female | 16 (61.50%) | 15 (65.2%) | 0.790 [a] |
| Male | 10 (38.50%) | 8 (34.8%) | |
| Age (years), Mean (SD) | 52.31 (9.26) | 56.13 (11.09) | 0.195 [b] |
| Height (cm), Mean (SD) | 157.74 (7.31) | 155.45 (6.35) | 0.251 [b] |
| Weight (Kg), Mean (SD) | 87.24 (12.37) | 84.54 (11.88) | 0.441 [b] |
| Body Mass Index (Kg/ $m^2$), Mean (SD) | 37.99 (5.60) | 37.07 (5.341) | 0.563 [b] |
| Affected Knee | | | |
| Left | 16 (61.50%) | 15 (65.2%) | 0.790 [a] |
| Right | 10 (38.50%) | 8 (34.8%) | |
| Level Of Education | | | |
| Educated | 9 (34.6%) | 10 (43.5%) | 0.830 [a] |
| Non-educated | 17 (65.4%) | 13 (56.5%) | |
| VAS, Mean (SD) | 6.39 (1.92) | 5.91 (1.78) | 0.474 [b] |
| SKFS, Median (IQR) | 61 (43.50 to 71.25) | 60 (49.00 to 70.00) | 0.912 [c] |
| ROM (°), Median (IQR) | 130° (124.50 to 135.75) | 130° (128.0 to 135.0) | 0.921 [c] |
| KC (cm), Mean (SD) | 43.30 (4.09) | 43.15 (4.89) | 0.885 [b] |
| Patient satisfaction (%), Median (IQR) | 35 (20.00 to 50.00) | 15 (0.00 to 50.00) | - |

G1, active group; G2, control group; Values are mean (SD) (if the data is numeric and normally distributed) or Median (IQR) (if the data are nominal or ordinal or is not normally distributed) for all variables unless stated to be a number of cases (percentage). SD, standard deviation; IQR, interquartile range; no significant difference between groups ($p > 0.05$); Statistical significance for the between group comparisons was tested using: a: Chi- square test, b: Independent Samples T-test, or c: Mann-Whitney test.

**Table 6-2 Test for distribution at the baseline (Shapiro-Wilk test)**

| | **G1** Sig. | **G2** Sig. |
|---|---|---|
| Age | 0.616 | **0.016** |
| Height | 0.088 | 0.365 |
| BMI | 0.332 | 0.356 |
| VAS | 0.145 | 0.162 |
| ROM | **0.010** | **0.002** |
| KC | 0.512 | 0.128 |
| G1, active group; G2, control group;<br>If the significance of the Shapiro-Wilk Test is > 0.05, the data are normally distributed. | | |

## 6.3 Within-group analyses

Within-group analyses were performed within each group of the study separately in order to investigate the efficacy of the treatment based on the change in the outcome scores during the course of the study. Changes from baseline versus each follow-up period were measured (i.e. baseline versus the 5th session, baseline versus the 9th session, baseline versus the week 6, and finally baseline versus 6 months after the last treatment session).

### 6.3.1 VAS

The VAS changes from baseline to each follow-up period were measured. In the active laser group and at the 5th session of the treatment, there was a statistically significant reduction on the VAS ($p < 0.001$). This improvement being statistically ($p < 0.001$) and clinically ($\geq 3$ scores mean difference) significant at the remaining 3 follow-up points. The mean total scores had decreased from 6.39 at baseline to 3.73 at the 5th session

assessment, to 3.15 at the 9th session, to 2.96 at week 6 and finally to 3.35 after 6 months from last treatment sessions. Previous results are presented in Table 6.3; see also Figure 6.1. Appendix X shows VAS scores for each participant from baseline to a 6 month assessment.

**Table 6-3 Changes in the outcomes from baseline over time for both groups with regard to VAS**

| | Mean (SD) | Mean difference (95% CI) | p-value [a] |
|---|---|---|---|
| **G1:** Baseline | 6.39 (1.92) | | |
| 5 sessions | 3.73 (2.12) | 2.65 (1.99 to 3.32) | < 0.001* |
| 9 sessions | 3.15 (1.74) | 3.23 (2.66 to 3.80) ** | < 0.001* |
| 6 weeks | 2.96 (1.64) | 3.42 (2.72 to 4.12) ** | < 0.001* |
| 6 months | 3.35 (1.78) | 3.04 (2.15 to 3.93) ** | < 0.001* |
| **G2:** Baseline | 5.91 (1.78) | | - |
| 5 sessions | 4.78 (2.34) | 1.13 (0.30 to 1.95) | 0.010* |
| 9 sessions | 3.78 (2.33) | 2.13 (1.27 to 2.98) | < 0.001* |
| 6 weeks | 4.28 (1.99) | 1.63 (0.79 to 2.46) | 0.001* |
| 6 months | 5.15 (2.21) | 0.76 (-0.17 to 1.69) | 0.103 |

[a] Paired Samples test, two-tailed.
G1, active group; G2, control group; Values are Mean (SD); (95% CI), confidence interval of the difference means; All comparisons were done versus the baseline values; *, represents a statistical significant difference ($p < 0.05$); **, represent clinically significant difference.

In the control group, statistically significant reduction was observed on the VAS scores at the 1st 3 follow-up points ($p < 0.05$). However, VAS scores of individuals in this group seems to have recurred OA symptoms after 6 months of stopping the placebo treatment ($p = 0.103$), with only (0.76) mean difference from the baseline (Table 6.3).

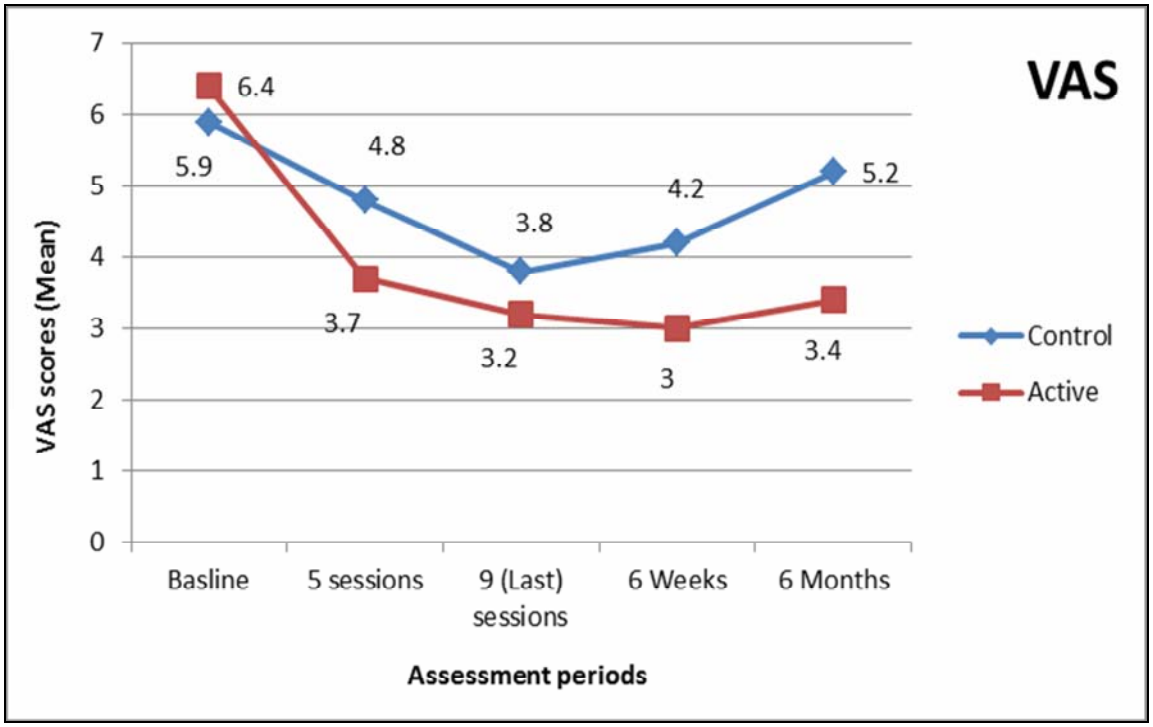


Figure 6-1 Change from baseline in mean scores of pain at movement which was measured by VAS for both groups

## 6.3.2 SKFS (total)

In the active laser group statistically significant reductions were detected in the SKFS scores in the post-treatment periods when compared to baseline for all comparisons ($p < 0.001$) (Table 6.4 and Figure 6.2). The median total scores had decreased from 61.00 at baseline to 37.00 at the 5th session assessment, to 26.00 at the 9th session, to 30.50 at week 6 and finally to 30.50 at 6 months from the last treatment sessions. Although scores slightly increased at the last two follow-up point's assessments, the improvement still continued reaching 50%, despite stopping the treatment by LLLT for 6 months (Table 6.4).

**Table 6-4 Changes in outcomes from baseline over time for both groups with regard to Saudi knee functional scale (total)**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** | | | |
| Baseline | 61.00 (43.50 to 71.25) | - | - |
| 5 sessions | 37.00 (19.50 to 53.50) | 24.00 | < 0.001* |
| 9 sessions | 26.00 (13.50 to 43.00) | 35.00 | < 0.001* |
| 6 weeks | 30.50 (12.00 to 43.50) | 30.50 | < 0.001* |
| 6 months | 30.50 (19.00 to 43.25) | 30.50 | < 0.001* |
| **G2:** | | | |
| Baseline | 60.00 (49.00 to 70.00) | - | - |
| 5 sessions | 45.00 (38.00 to 54.00) | 15.00 | 0.001* |
| 9 sessions | 41.00 (29.00 to 53.00) | 19.00 | < 0.001* |
| 6 weeks | 40.00 (29.00 to 54.00) | 20.00 | < 0.001* |
| 6 months | 51.00 (33.00 to 55.00) | 9.00 | 0.004* |

[a] Wilcoxon signed-rank test, two-tailed
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

Similar results were found in the control group; statistically significant improvement was observed in the SKFS at all follow-up points ($p < 0.05$) (Table 6.4 and Figure 6.2). The median total scores had decreased from 60.00 at baseline to 45.00 at the 5th session assessment; to 41.00 at the 9th session; and to 40.00 after 6 weeks. However, at 6

months from the last treatment sessions, the median total scores had increased again to reach 51.00 (Table 6.4). Nevertheless, both groups showed statistically significant improvement in the SKFS, and the improvement was greater in the active laser group. For example, the improvement of KOA symptoms in the active laser group had reached 50% at 6 months after the last session of the treatment, whereas, in the placebo laser group, the improvement was only 15% for the same period of the assessment. Appendix XI shows SKFS scores for each participant from baseline to a 6 month assessment.

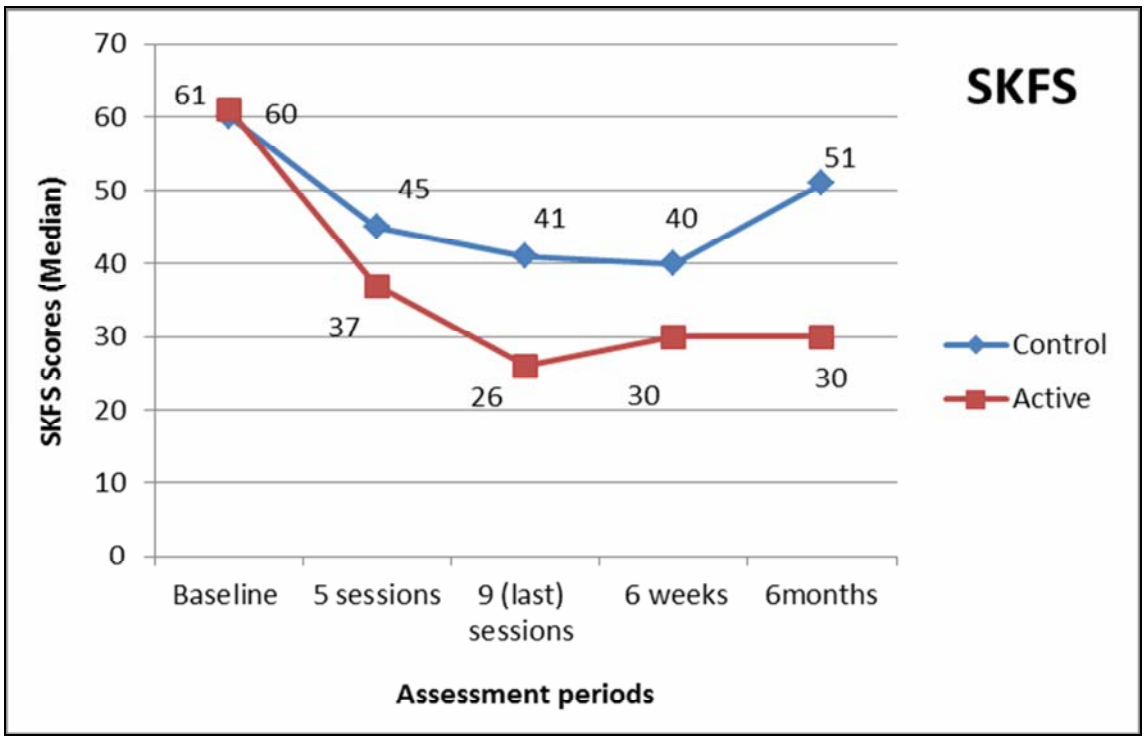


Figure 6-2 Change from baseline in median scores of SKFS for both groups

### 6.3.3 SKFS subscales

As stated previously (Section 5.5.2), the SKFS index contains five subscales (pain, stiffness, physical function, social function, and emotional function). The Wilcoxon signed-rank test was used for these analyses. Each follow-up period was analysed versus the baseline. In the active group, analysis indicated that there were statistically significant improvements ($p < 0.05$) for all five subscales (Tables 6.5 to 6.9). Similar

findings were detected regarding the control group, and the improvements were statistically significant for all five subscales ($p < 0.05$) (Tables 6.5 to 6.9), except with regard to the social function subscale at the 5th session and at the 9th session assessment period ($p > 0.05$) (Table 6.8).

**Table 6-5 Changes in outcomes from baseline over time for both groups with regard to SKFS (Pain) subscale.**

| | Median(IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** | | | |
| Baseline | 17.00 (13.75 to 21.25) | - | - |
| 5 sessions | 11.00(6.75 to 14.50) | 6.00 | < 0.001* |
| 9 sessions | 8.00 (4.75 to 12.00) | 9.00 | < 0.001* |
| 6 weeks | 8.50 (4.75 to 13.50) | 8.50 | < 0.001* |
| 6 months | 10. (6.75 to 13.00) | 7.00 | < 0.001* |
| **G2:** | | | |
| Baseline | 17.00 (15.00 to 21.00) | - | - |
| 5 sessions | 11.00 (9.00 to16. 00) | 6.00 | 0.001* |
| 9 sessions | 10.00 (9.00 to 14.00) | 7.00 | < 0.001* |
| 6 weeks | 13.00 (9.00 to 16.00) | 4.00 | 0.002* |
| 6 months | 15.00 (12.00 to 18.00) | 2.00 | 0.040* |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; pain subscale (score 0 to 32); All comparisons were done versus the baseline values; *, represent a significant difference ($p < 0.05$).

**Table 6-6 Changes in outcomes from baseline over time for both groups with regard to SKFS (Stiffness) subscale**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** | | | |
| Baseline | 5.00 (4.00 to 6.00) | - | - |
| 5 sessions | 3.00 (2.00 to 5.25) | 2.00 | 0.001* |
| 9 sessions | 2.00 (0.00 to 3.00) | 3.00 | < 0.001* |
| 6 weeks | 2.00 (1.00 to 4.00) | 3.00 | < 0.001* |
| 6 months | 2.00 (1.00 to 4.00) | 3.00 | < 0.001* |
| **G2:** | | | |
| Baseline | 6.00 (4.00 to 6.00) | - | - |
| 5 sessions | 4.00 (1.00 to 6.00) | 2.00 | 0.002* |
| 9 sessions | 3.00 (1.00 to 6.00) | 3.00 | 0.001* |
| 6 weeks | 4.00 (2.00 to 5.00) | 2.00 | 0.005* |
| 6 months | 2.00 (1.00 to 4.00) | 4.00 | 0.001* |

[a] Wilcoxon signed-rank test, two-tailed
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; stiffness subscale (score 0 to8); All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

**Table 6-7 Changes in outcomes from baseline over time for both groups with regard to SKFS (Physical function) subscale**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1** | | | |
| Baseline | 27.00 (19.75 to 33.50) | | |
| 5 sessions | 16.00 (8.75 to 24.25) | 11.00 | < 0.001* |
| 9 sessions | 12.00 (6.75 to 19.00) | 15.00 | < 0.001* |
| 6 weeks | 14.00 (6.75 to 23.00) | 13.00 | < 0.001* |
| 6 months | 13.50 (7.75 to 18.00) | 13.50 | < 0.001* |
| **G2** | | | |
| Baseline | 27.00 (21.00 to 30.00) | | |
| 5 sessions | 21.00 (16.00 to 26.00) | 6.00 | 0.003* |
| 9 sessions | 19.00 (14.00 to 23.00) | 8.00 | < 0.001* |
| 6 weeks | 19.00 (14.00 to 23.00) | 8.00 | 0.001* |
| 6 months | 23.00 (16.00 to 27.00) | 4.00 | 0.028* |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; physical function subscale (score 0 to 48); All comparisons were done versus the baseline values; *, represent a significant difference ($p < 0.05$).

**Table 6-8 Changes in outcomes from baseline over time for both groups with regard to SKFS (Social functions) subscale**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** | | | |
| Baseline | 6.00 (0.00 to 8.00) | - | - |
| 5 sessions | 3.00 (0.00 to 6.25) | 3.00 | 0.006* |
| 9 sessions | 1.00 (0.00 to 6.00) | 5.00 | 0.001* |
| 6 weeks | 0.00 (0.00 to 6.00) | 6.00 | 0.001* |
| 6 months | 3.00 (0.75 to 4.25) | 3.00 | 0.011* |
| **G2:** | | | |
| Baseline | 6.00 (4.00 to 8.00) | - | - |
| 5 sessions | 5.00 (3.00 to 8.00) | 1.00 | 0.087 |
| 9 sessions | 3.00 (1.00 to 6.00) | 3.00 | 0.058 |
| 6 weeks | 3.00 (0.00 to 6.00) | 3.00 | 0.036* |
| 6 months | 5.00 (0.00 to 6.00) | 1.00 | 0.019* |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; social subscale (score 0 to 12); All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

**Table 6-9 Changes in outcomes from baseline over time for both groups with regard to SKFS (Emotional function) subscale**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** | | | |
| Baseline | 6.00 (2.75 to 9.00) | - | - |
| 5 sessions | 2.00 (0.00 to 6.00) | 4.00 | < 0.001* |
| 9 sessions | 0.00 (0.00 to 3.25) | 6.00 | < 0.001* |
| 6 weeks | 0.50 (0.00 to 5.00) | 5.50 | < 0.001* |
| 6 months | 2.00 (0.00 to 4.00) | 4.00 | 0.001* |
| **G2:** | | | |
| Baseline | 6.00 (4.00 to 9.00) | - | - |
| 5 sessions | 5.00 (0.00 to 6.00) | 1.00 | 0.006* |
| 9 sessions | 0.00 (0.00 to 3.25) | 6.00 | 0.004* |
| 6 weeks | 1.00 (0.00 to 6.00) | 5.00 | < 0.001* |
| 6 months | 4.00 (2.00 to 6.00) | 2.00 | 0.003* |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; emotional function subscale (score 0 to 12); All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

### 6.3.4 ROM

Because the data collected for the degree of active knee flexion were not normally distributed (Table 6.2), the Wilcoxon signed-rank test was used in the analyses. There was a statistically significant improvement with regards to the ROM for individuals in the active laser group when the baseline-versus-follow-up periods were compared ($p < 0.05$) (Table 6.10). The median total scores had increased with a median difference (6.50) at the 5th session assessment; with a median difference (8) at the 9th session; with a median difference (7) at 6 weeks after; and finally with a median difference (6) at 6 months from the last treatment sessions (Table 6.10 and Figure 6.3). That means that the ROM of participants remained improved in this group. Appendix XIV shows the ROM scores for each patient from baseline to a six month assessment.

In the control group, statistically significant increases in the ROM were seen at the 1st and 2nd follow-up periods, compared to the baseline values ($p < 0.05$). The median total scores had increased with a median difference (2) at the 5th session assessment; with a median difference (5) at the 9th session. However, this improvement was regressed at week 6 to be not significant ($p > 0.05$), and it was back to the same level at six months after the last treatment session ($p > 0.05$) (Table 6.10 and Figure 6.3).

**Table 6-10 Changes in outcomes from baseline over time for both groups with regard to ROM.**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** Baseline | 130.00 (124.50 to 135.75) | - | - |
| 5 sessions | 136.50 (132.75 to 140.50) | 6.50 | <0.001* |
| 9 sessions | 138.00 (131.75 to 144.25) | 8.00 | <0.001* |
| 6 weeks | 137.00 (130.00 to 140.00) | 7.00 | 0.001* |
| 6 months | 136.00 (134.25 to 140.00) | 6.00 | <0.001* |
| **G2:** Baseline | 130.00 (128.00 to 135.00) | - | - |
| 5 sessions | 132.00 (130.00 to 139.00) | 2.00 | 0.021* |
| 9 sessions | 135.00 (130.00 to 138.00) | 5.00 | 0.029* |
| 6 weeks | 135.00 (125.00 to 140.00) | 5.00 | 0.102 |
| 6 months | 130.00 (127.00 to 138.00) | 0.00 | 0.663 |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

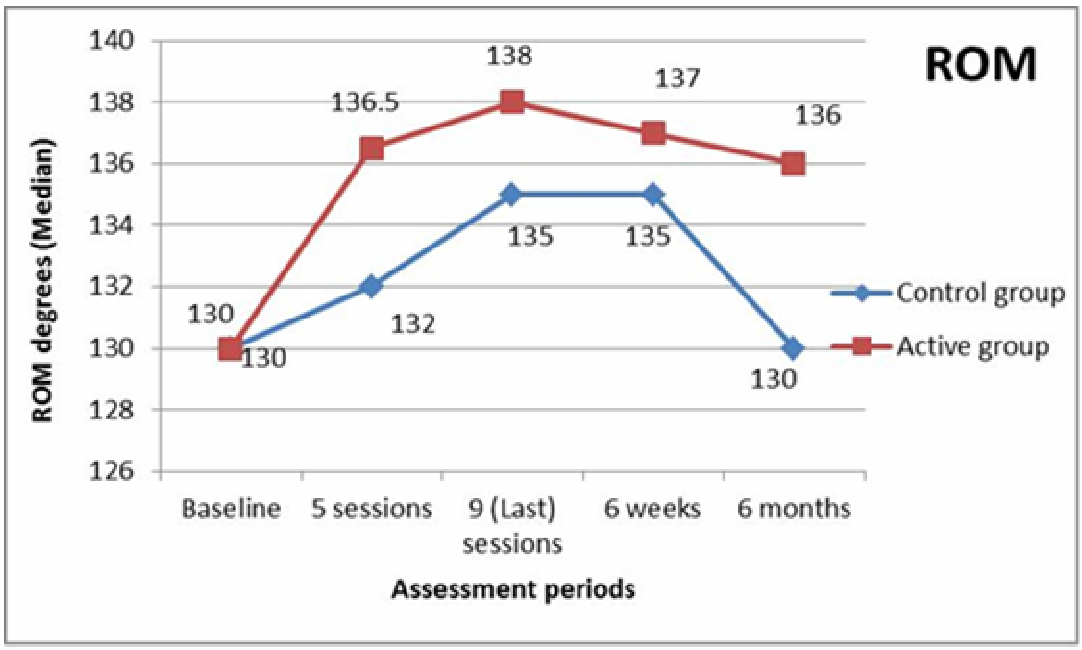


Figure 6-3 Change from baseline in median scores of ROM for both groups

### 6.3.5 KC

Participants in the active laser group showed no statistically significant improvement ($p > 0.05$) in the KC at any follow-up period when compared with the baseline values (Table 6.11 and Figure 6.4). In contrast, participants in the control group showed statistically significant improvement at the 9th session assessment and at the 6 month assessment ($p < 0.05$). At the 5th week and 6 week follow-up assessment, there was no statistically significant improvement ($p > 0.05$) (Table 6.11 and Figure 6.4). Appendix XV shows KC scores for each patient from baseline to a 6 month assessment.

**Table 6-11 Changes in outcomes from baseline over time for both groups with regard to KC.**

| | Mean (SD) | Mean difference (95% CI) | p-value [a] |
|---|---|---|---|
| **G1:** Baseline | 43.34 (4.09) | | - |
| 5 sessions | 43.12 (4.16) | -0.22 (-0.49 to 0.05) | 0.102 |
| 9 sessions | 43.06 (4.10) | -0.28 (-0.78 to 0.21) | 0.254 |
| 6 weeks | 43.27 (4.09) | -0.06 (-0.49 to 0.35) | 0.737 |
| 6 months | 43.21 (4.33) | -0.13 (-0.64 to 0.39) | 0.614 |
| **G2:** Baseline | 43.15 (4.89) | | - |
| 5 sessions | 42.78 (4.72) | -0.37 (-0.78 to 0.04) | 0.074 |
| 9 sessions | 42.59 (4.61) | -0.57 (-0.91 to 0.23 ) | 0.002* |
| 6 weeks | 42.91 (4.79) | -0.24 (-0.65 to 0.18 ) | 0.241 |
| 6 months | 42.51 (4.79) | -0.64 (-1.26 to 0.02 ) | 0.043* |

[a] Paired Student T-test, two-tailed.
G1, active group; G2, control group; Values are Mean (SD); (95% CI), confidence interval of the difference means; All comparisons were done versus the baseline values; *, represents a significant difference ($p < 0.05$).

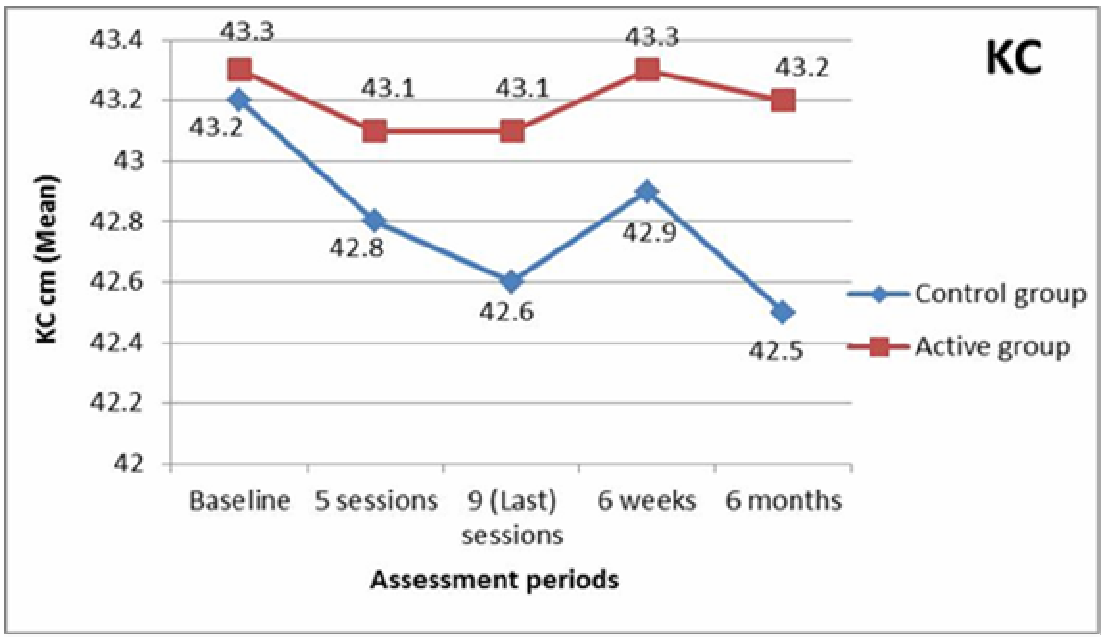


Figure 6-4 Change from baseline in median scores of KC for both groups.

### 6.3.6 Patient satisfaction

Patients in both groups of the study were asked to rate their satisfaction with the intervention that they received. Patient satisfaction was analysed by comparing the value of the 5th session assessment period versus the remaining three follow-up periods. In the active laser group, statistically significant differences have been noted at all assessment periods ($p < 0.05$) (Table 6.12 and Figure 6.5). An average patient satisfaction of individuals in the active laser group was 36% at the 5th assessment period, which increased to 46.50% at the 9th session assessment, 50% at 6 weeks assessment, and 53% at 6 months after the last treatment session by active LLLT (Table 6.12 and Figure 6.5).

**Table 6-12 Changes in outcomes from baseline over time for both groups with regard to patient satisfaction.**

| | Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|
| **G1:** 5 sessions | 35.00 (20.00 to 50.00) | - | - |
| 9 sessions | 50.00 (23.75 to 65.00) | 15.00 | 0.003* |
| 6 weeks | 47.50 (30.00 to 70.00) | 12.50 | 0.004* |
| 6 months | 50.00 (30.00 to 76.25) | 15.00 | 0.003* |
| **G2:** 5 sessions | 15.00 (00.00 to 50.00) | - | - |
| 9 sessions | 40.00 (10.00 to 60.00) | 25.00 | 0.001* |
| 6 weeks | 45.00 (15.00 to 50.00) | 30.00 | 0.001* |
| 6 months | 20.00 (10.00 to 30.00) | 05.00 | 0.678 |

[a] Wilcoxon signed-rank test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; All comparisons were done versus the baseline values (5 sessions, assumed to be the baseline); *, represents a significant difference ($p < 0.05$).
**Table presents percentage satisfaction.

Regarding the control group, the average patient satisfaction was 23% at the 5th assessment period, which was increased to 37% at the 9th session assessment ($p < 0.05$), and up to 38% ($p < 0.05$) at week 6 of the assessment. However, the satisfaction decreased to 25% at six months after the last treatment session, and the result became statistically non-significant ($p > 0.05$). For more details, see Table 6.12 and Figure 6.5. Appendix XVI shows patient satisfaction scores for each patient from baseline to a 6 month assessment.

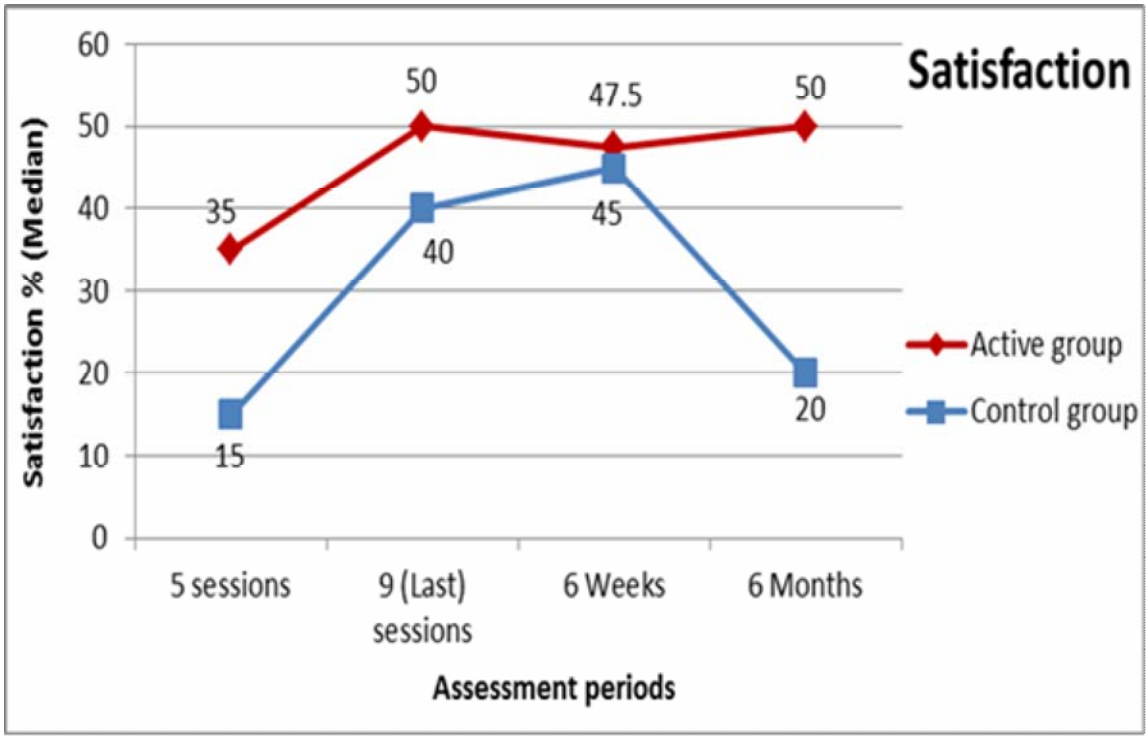


Figure 6-5 Change from baseline (5th session) in median scores of patient satisfaction for both groups.

## 6.4 Between-groups analyses

Between-groups analyses were performed between the two groups of the study, Group 1 and Group 2, in order to investigate if there were any statistical differences between the two groups. Then, if there were significant differences between them, the superiority of the treatment type (active laser or placebo laser) would be investigated. The Mann-Whitney U test was applied as a non-parametric test for data that failed to fulfil the requirements of the parametric test, and the independent samples t-test was applied to data that fulfilled the parametric test requirements. As stated previously in this chapter (Section 6.2), there was no difference between the two groups in the baseline data with regards to all of the baseline outcome measurements. In addition to the baseline comparisons, the change in each of the outcome variables at the 5th session, at the 9th session, at week 6, and after six months of the last treatment session of both groups was compared between groups.

### 6.4.1 VAS

Comparisons between the mean VAS scores of the two groups are displayed below in Table 6.13; the result is expressed as mean (SD) and mean difference (95% CI). Statistically significant differences were detected between groups in the VAS after 6 weeks and after 6 months of the end of treatment ($p < 0.05$) in favour of the active laser group. The between-groups analyses showed no statistically significant difference between the two groups in the VAS scores at the 5th session and at the 9th session ($p > 0.05$).

**Table 6-13 Changes in the outcomes between both groups with regard to the VAS**

| | **G1** Mean (SD) | **G2** Mean (SD) | Mean difference (95% CI) | p-value [a] |
|---|---|---|---|---|
| Baseline | 6.39 (1.92) | 5.91 (1.78) | 0.47 (-0.58 to 1.52) | 0.372 |
| 5 sessions | 3.73 (2.12) | 4.78 (2.34) | -1.05 (-2.34 to 0.23) | 0.106 |
| 9 sessions | 3.15 (1.74) | 3.78 (2.34) | -0.63 (-1.80 to 0.55) | 0.287 |
| 6 weeks | 2.96 (1.64) | 4.28 (1.99) | -1.32 (-2.37 to -0.27) | 0.014* |
| 6 months | 3.35 (1.78) | 5.15 (2.21) | -1.80 (-2.95 to -0.66) | 0.003* |

[a] Independent Samples Test, two-tailed.
G1, active group; G2, control group; Values are Mean (SD); (95% CI), confidence interval of the difference means; *, represents a significant difference ($p < 0.05$).

## 6.4.2 SKFS (total)

Comparison of the two groups showed significant statistical reduction in the SKFS scores in the active laser group compared to the placebo laser group at the 9th session ($p = 0.035$). This significant improvement was increased at 6 months after the last treatment session ($p = 0.006$). No significant difference between the two groups was noted when comparing the change at the 5th session and at week 6 ($p > 0.05$) (Table 6.14).

**Table 6-14 Changes in the outcomes between both groups with regard to the SKFS (total)**

| SKFS (total) | G1 Median (IQR) | G2 Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 61.00 (43.50 to 71.25) | 60.00 (49.00 to 70.00) | 1.00 | 0.912 |
| 5 sessions | 37.00 (19.50 to 53.50) | 45.00 (38.00 to 54.00) | -8.00 | 0.141 |
| 9 sessions | 26.00 (13.50 to 43.00) | 41.00 (29.00 to 53.00) | -15.00 | 0.035* |
| 6 weeks | 30.50 (12.00 to 43.50) | 40.00 (29.00 to 54.00) | - 09.50 | 0.054 |
| 6 months | 30.50 (19.00 to 43.25) | 51.00 (33.00 to 55.00) | - 20.50 | 0.006* |

[a] Mann-Whitney U test, two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; *, represents a significant difference ($p < 0.05$).

## 6.4.3 SKFS subscales

Comparisons between the median scores of the two groups with respect to subscales of the SKFS are displayed below in Tables 6.15–6.19. Comparison of the two groups showed a statistically significant difference in the pain subscale favouring the active laser group at the week 6 assessment and after 6 months ($p < 0.05$). Otherwise, no statistically significant differences were detected between the two groups for the other periods ($p > 0.05$) (Table 6.15).

**Table 6-15 Changes in the outcomes between both groups with regard to the SKFS (Pain) subscale**

| SKFS (Pain) | G1 Median (IQR) | G2 Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 17.00 (13.75 to 21.25) | 17.00 (15.00 to 21.00) | 0.00 | 0.794 |
| 5 sessions | 11.00 (6.75 to 14.5) | 11.00 (9.00 to16. 00) | 0.00 | 0.451 |
| 9 sessions | 8.00 (4.75 to 12.00) | 10.00 (9.00 to 14.00) | -2.00 | 0.082 |
| 6 weeks | 8.50 (4.75 to 13.50) | 13.00 (9.00 to 16.00) | -4.50 | 0.035* |
| 6 months | 10.00 (6.75 to 13.00) | 15.00 (12.00 to 18.00) | -5.00 | 0.001* |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; pain subscale (score 0 to 32); *, represents a significant difference ($p < 0.05$).

The stiffness subscale between-groups analyses showed statistically significant difference favouring the active laser group at the 9th session and at week 6 ($p < 0.05$); all other comparisons for the remaining assessment periods showed no statistical significant difference between the groups ($p > 0.05$) (Table 6.16).

**Table 6-16 Changes in the outcomes between both groups with regard to the SKFS (Stiffness) subscale.**

| SKFS (Stiffness) | G1 Median (IQR) | G2 Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 5.00 (4.00 to 6.00) | 6.00 (4.00 to 6.00) | -1.00 | 0.792 |
| 5 sessions | 3.00 (2.00 to 5.25) | 4.00 (1.00 to 6.00) | -1.00 | 0.823 |
| 9 sessions | 2.00 (0.00 to 3.00) | 3.00 (1.00 to 6.00) | -1.00 | 0.041* |
| 6 weeks | 2.00 (1.00 to 4.00) | 4.00 (2.00 to 5.00) | -2.00 | 0.048* |
| 6 months | 2.00 (1.00 to 4.00) | 2.00 (1.00 to 4.00) | 0.00 | 0.399 |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; stiffness subscale (score 0 to 8); *, represents a significant difference ($p < 0.05$).

The active laser group showed statistically significant, differences in median scores of the physical function subscale were identified between the two groups at the 9th session assessment period ($p = 0.022$). This significant difference continued until the next assessment period, week 6, with a slight decrease ($p = 0.043$). However, this significant difference considerably increased after 6 months of the last treatment session ($p = 0.001$). No statistically significant differences between the groups ($p > 0.05$) were found for the rest of the comparison periods (Table 6.17).

**Table 6-17 Changes in the outcomes between both groups with regard to the SKFS (Physical function) subscale.**

| SKFS (Physical function) | G1 Median (IQR) | G2 Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 27.00 (19.75 to 33.50) | 27.00 (21.00 to 30.00) | 0.00 | 0.817 |
| 5 sessions | 16.00 (8.75 to 24.25) | 21.00 (16.00 to 26.00) | - 5.00 | 0.111 |
| 9 sessions | 12.00 (6.75 to 19.00) | 19.00 (14.00 to 23.00) | -7.00 | 0.022* |
| 6 weeks | 14.00 (6.75 to 23.00) | 19.00 (14.00 to 23.00) | -5.00 | 0.043* |
| 6 months | 13.50 (7.75 to 18.00) | 23.00 (16.00 to 27.00) | -9.50 | 0.001* |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; physical function subscale (score 0 to 48); *, represents a significant difference ($p < 0.05$).

With respect to social function subscale, the result showed no statistically significant difference between the groups at any time during follow-up ($p > 0.05$); although the result came close to being significant at the week-6 assessment period ($p = 0.053$) (Table 6.18). A similar result has been found with regards to the emotional function subscale, where no statistically significant difference between the groups was found in any of the follow-up assessment periods ($p > 0.05$) (Table 6.19).

**Table 6-18 Changes in the outcomes between both groups with regard to the SKFS (Social function) subscale.**

| SKFS (Social function) | **G1** Median (IQR) | **G2** Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 6.00 (0.00 to 8.00) | 6.00 (4.00 to 8.00) | 0.00 | 0.737 |
| 5 sessions | 3.00 (0.00 to 6.25) | 5.00 (3.00 to 8.00) | -2.00 | 0.162 |
| 9 sessions | 1.00 (0.00 to 6.00) | 3.00 (1.00 to 6.00) | -2.00 | 0.086 |
| 6 weeks | 0.00 (0.00 to 6.00) | 3.00 (0.00 to 6.00) | -3.00 | 0.053 |
| 6 months | 3.00 (0.75 to 4.25) | 5.00 (0.00 to 6.00) | -2.00 | 0.202 |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; social subscale (score 0 to 12); *, represents a significant difference ($p < 0.05$).

**Table 6-19 Changes in the outcomes between both groups with regard to the SKFS (Emotional function) subscale.**

| SKFS (Emotional function) | G1 Median (IQR) | G2 Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 6.00 (2.75 to 9.00) | 6.00 (4.00 to 9.00) | 0.00 | 0.784 |
| 5 sessions | 6.00 (0.00 to 6.00) | 5.00 (0.00 to 6.00) | 1.00 | 0.279 |
| 9 sessions | 0.00 (0.00 to 3.25) | 2.00 (0.00 to 7.00) | -2.00 | 0.101 |
| 6 weeks | 0.50 (0.00 to 5.00) | 1.00 (0.00 to 6.00) | -0.50 | 0.681 |
| 6 months | 2.00 (0.00 to 4.00) | 4.00 (2.00 to 6.00) | -2.00 | 0.164 |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; emotional function subscale (score 0 to 12); *, represents a significant difference ($p < 0.05$).

## 6.4.4 ROM

There was no statistically significant difference between the two groups with regards to ROM at all follow-up assessment periods ($p > 0.05$), except at 6 months after the last treatment session which showed statistically significant improvement in favour of the active laser group ($p < 0.05$) (Table 6.20).

**Table 6-20 Change in the outcomes between groups with regard to ROM.**

| | **G1** Median (IQR) | **G2** Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| Baseline | 130.00 (124.50 to 135.75) | 130.00 (128.00 to 135.00) | 0.00 | 0.848 |
| 5 sessions | 136.50 (132.75 to 140.50) | 132.00 (130.00 to 139.00) | 4.50 | 0.112 |
| 9 sessions | 138.00 (131.75 to 144.25) | 135.00 (130.00 to 138.00) | 3.00 | 0.101 |
| 6 weeks | 137.00 (130.00 to 140.00) | 135.00 (125.00 to 140.00) | 2.00 | 0.308 |
| 6 months | 136.00 (134.25 to 140.00) | 130.00 (127.00 to 138.00) | 6.00 | 0.019* |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; *, represents a significant difference ($p < 0.05$).

## 6.4.5 KC

The between-groups analyses showed that there was no statistically significant difference ($p > 0.05$) between the two groups of the study with respect to KC at all 4 follow-up assessment periods (Table 6.21 and Figure 6.4) .

**Table 6-21 Changes in the outcomes between both groups with regard to KC**

| | G1<br>Mean (SD) | G2<br>Mean (SD) | Mean difference (95% CI) | p-value [a] |
|---|---|---|---|---|
| Baseline | 43.34 (4.09) | 43.15 (4.89) | 0.19 (-2.39 to 2.77) | 0.885 |
| 5 sessions | 43.12 (4.16) | 42.78 (4.72) | 0.33 (-2.22 to 2.88) | 0.794 |
| 9 sessions | 43.06 (4.10) | 42.59 (4.61) | 0.47 (-2.04 to 2.98) | 0.708 |
| 6 weeks | 43.27 (4.09) | 42.91 (4.79) | 0.36 (-2.19 to 2.91) | 0.780 |
| 6 months | 43.21 (4.33) | 42.51 (4.79) | 0.70 (-1.91 to 3.33) | 0.592 |

[a] Independent t-test, two-tailed.
G1, active group; G2, control group; Values are Mean (SD); (95% CI), confidence interval of the difference means; *, represents a significant difference ($p < 0.05$).

## 6.4.6 Patient satisfaction

After the first 4 sessions, more specifically, at the 5th session assessment period, each patient was asked about her/his satisfaction with the benefit they have gained from the treatment provided. Comparisons between groups for this period showed statistically significant difference between the two groups ($p < 0.05$) in favour of the active laser group (Table 6.22). Although the active laser group showed more consistent increases in their satisfaction, the results showed no statistically significant between the two groups at the 9th session assessment period and at week 6 of the assessment ($p > 0.05$). However, at six months after the last treatment session, participants in the active laser group showed considerably greater satisfaction than those in the placebo laser group did ($p < 0.001$) (Table 6.22).

**Table 6-22 Changes in the outcomes between both groups with regard to patient satisfaction.**

| | G1<br>Median (IQR) | G2<br>Median (IQR) | Median difference | p-value [a] |
|---|---|---|---|---|
| 5 sessions | 35.00 (20.00 to 50.00) | 15.00 (00.00 to 50.00) | 20.00 | 0.033* |
| 9 sessions | 50.00 (23.75 to 65.00) | 40.00 (10.00 to 60.00) | 10.00 | 0.184 |
| 6 weeks | 47.50 (30.00 to 70.00) | 45.00 (15.00 to 50.00) | 2.50 | 0.167 |
| 6 months | 50.00 (30.00 to 76.25) | 20.00 (10.00 to 30.00) | 30.00 | <0.001* |

[a] Mann-Whitney U test two-tailed.
G1, active group; G2, control group; Values are Median (IQR); (IQR), interquartile range; *, represents a significant difference ($p < 0.05$).

**Table presents percentage satisfaction.

## 6.5 Assessment of possible Correlation and relationships between variables

The following section describes the investigation of possible correlations between different variables, such as age, BMI, patient satisfaction, ROM, KC, VAS, and SKFS. The analysis has been used to assess whether variables had a relationship and if so, to quantify the strength of the relationship between variables if required. The Pearson correlation test has been used for numeric data, whereas Spearman's rho correlation test was used for non-numeric data. If there is no significant correlation or weak correlation between some variables, it is still relevant to test them, the reasons for which will be discussed in Chapter 7 (Section 7.3).

## 6.5.1 Correlation between different variables and VAS

Table 6.23 below shows that there was no significant correlation between any variables and the VAS at any time in both groups of the study.

**Table 6-23 Correlation table between age, BMI and VAS for both groups of the study**

| | Correlation [a] | Baseline | 5 Sessions | Last Session | 6 Weeks | 6 Months |
|---|---|---|---|---|---|---|
| **G1** | | | | | | |
| Age | r. | 0.186 | 0.125 | 0.091 | 0.371 | 0.196 |
| | Sig. | 0.362 | 0.542 | 0.657 | 0.062 | 0.338 |
| BMI | r. | -0.166 | -0.068 | 0.035 | -0.366 | -0.139 |
| | Sig. | 0.418 | 0.742 | 0.866 | 0.066 | 0.498 |
| **G2** | | | | | | |
| Age | r. | 0.017 | 0.146 | 0.276 | 0.244 | 0.128 |
| | Sig. | 0.937 | 0.505 | 0.202 | 0.261 | 0.561 |
| BMI | r. | 0.261 | 0.072 | -0.078 | -0.067 | -0.217 |
| | Sig. | 0.229 | 0.743 | 0.725 | 0.76 | 0.32 |

[a] Pearson correlation test; r, correlation coefficient; Sig., significant; G1, active group; G2, control group.

## 6.5.2 Correlation between different variables and SKFS

Table 6.24 below shows that, in the active laser group, there was only a moderate significant positive correlation between age and SKFS at the last session assessment period. With regard to the control group, there was no significant correlation between any variables and the SKFS at any time.

**Table 6-24 Correlation table between age, BMI and SKFS for both groups of the study, significant correlations are bolded.**

| | Correlation [a] | Baseline | 5 Sessions | Last Session | 6 Weeks | 6 Months |
|---|---|---|---|---|---|---|
| **G1** | | | | | | |
| Age | r. | 0.184 | 0.318 | **0.413*** | 0.388 | 0.214 |
| | Sig. | 0.368 | 0.114 | **0.036** | 0.05 | 0.294 |
| BMI | r. | 0.063 | 0.02 | 0.094 | -0.008 | 0.244 |
| | Sig. | 0.76 | 0.922 | 0.648 | 0.968 | 0.229 |
| **G2** | | | | | | |
| Age | r. | 0.105 | 0.255 | 0.31 | 0.251 | 0.376 |
| | Sig. | 0.635 | 0.24 | 0.15 | 0.247 | 0.077 |
| BMI | r. | 0.352 | 0.33 | 0.116 | 0.027 | -0.149 |
| | Sig. | 0.1 | 0.124 | 0.599 | 0.902 | 0.497 |

[a] Spearman's rho correlation test; r, correlation coefficient; Sig., significant;*, significant correlation; G1, active group; G2, control group.

## 6.5.3 Correlation between different variables and ROM

In the active laser group, there was no significant correlation between ROM and age, and BMI at any time of the assessment (Table 6.25). However, with regard to the control group, a moderate significant negative correlation was noted between BMI and the ROM at baseline, last treatment session, and at week 6 assessment periods (Table 6.25).

**Table 6-25 Correlation table between age, BMI, and ROM for both groups of the study, significant correlations are bolded.**

| | Correlation [a] | Baseline | 5 Sessions | Last Session | 6 Weeks | 6 Months |
|---|---|---|---|---|---|---|
| **G1** | | | | | | |
| Age | r. | -0.08 | -0.004 | -0.033 | -0.121 | -0.244 |
| | Sig. | 0.699 | 0.986 | 0.873 | 0.556 | 0.23 |
| BMI | r. | -0.07 | -0.255 | -0.202 | -0.095 | -0.163 |
| | Sig. | 0.735 | 0.208 | 0.322 | 0.644 | 0.425 |
| **G2** | | | | | | |
| Age | r. | 0.01 | -0.019 | 0.025 | 0.049 | 0.067 |
| | Sig. | 0.963 | 0.931 | 0.909 | 0.823 | 0.76 |
| BMI | r. | **-0.470*** | -0.343 | **-0.456*** | **-0.433*** | -0.269 |
| | Sig. | **0.024** | 0.11 | **0.029** | **0.039** | 0.214 |

[a] Spearman's rho correlation test; r, correlation coefficient; Sig., significant; *, significant correlation.
G1, active group; G2, control group.

## 6.5.4 Correlation between different variables and KC

Table 6.26 below shows that, in the active laser group, there was a moderate significant positive correlation between BMI and KC at the baseline, last treatment session, and at 6 months assessment periods. With regard to the control group, there was a strong significant positive correlation between BMI and KC at all assessment periods.

**Table 6-26 Correlation table between age, BMI and KC for both groups of the study, significant correlations are bolded**

| | Correlation [a] | Baseline | 5 Sessions | Last Session | 6 Weeks | 6 Months |
|---|---|---|---|---|---|---|
| **G1** | | | | | | |
| Age | r. | -0.069 | -0.064 | -0.12 | -0.075 | -0.094 |
| | Sig. | 0.739 | 0.755 | 0.558 | 0.716 | 0.648 |
| BMI | r. | **0.395*** | 0.38 | **0.459*** | 0.38 | **0.409*** |
| | Sig. | **0.046** | 0.056 | **0.018** | 0.055 | **0.038** |
| **G2** | | | | | | |
| Age | r. | -0.143 | -0.122 | -0.126 | -0.176 | -0.159 |
| | Sig. | 0.514 | 0.579 | 0.566 | 0.422 | 0.469 |
| BMI | r. | **0.537**** | **0.533**** | **0.519*** | **0.506*** | **0.520*** |
| | Sig. | **0.008** | **0.009** | **0.011** | **0.014** | **0.011** |

[a] Pearson correlation test; r, correlation coefficient; Sig., significant; *, significant correlation; **, strong significant correlation; G1, active group; G2, control group,

## 6.5.5 Correlation between different variables and patient satisfaction

In the active laser group, there was a strong significant negative correlation between age and patient satisfaction at six month assessment period (Table 6.27). In the control group, a moderate significant positive correlation was noted between BMI and patient satisfaction at the six month assessment (Table 6.27).

Table 6-27 Correlation table between age, BMI and patient satisfaction for both groups of the study, significant correlations are bolded.

| | Correlation [a] | 5 Sessions | Last Session | 6 Weeks | 6 Months |
|---|---|---|---|---|---|
| **G1** | | | | | |
| Age | r. | -0.008 | -0.068 | -0.086 | **-0.525**** |
| | Sig. | 0.967 | 0.74 | 0.676 | **0.006** |
| BMI | r. | -0.2 | -0.304 | -0.033 | -0.023 |
| | Sig. | 0.326 | 0.131 | 0.872 | 0.912 |
| **G2** | | | | | |
| Age | r. | -0.309 | -0.313 | -0.285 | 0.05 |
| | Sig. | 0.151 | 0.146 | 0.188 | 0.82 |
| BMI | r. | -0.017 | 0.261 | 0.294 | **0.478*** |
| | Sig. | 0.94 | 0.229 | 0.173 | **0.021** |

[a] Spearman's rho correlation test; r, correlation coefficient; Sig., significant; *, significant correlation; **, strong significant correlation; G1, active group; G2, control group.

## 6.5.6 Subgroup analyses

In the current study, the subgroup analyses were undertaken after the results of the study had been compiled. They were not based on a primary study outcome, therefore it has not been powered to detect subgroup effects. In the current study, analyses were undertaken to investigate if a response to the treatment is different across particular groups of patients. The interaction effect between subgroup and treatment was tested using UAV test. The independent variables for the UAV were age, gender, BMI, and level of education. The two dependent variables were VAS and SKFS scores. At each time point two models were fitted: one with main effects of treatment and the independent variables and a second including interactions between treatment and these variables.

Brookes *et al.* (2001) reported that subgroup testing requires the data to be split and these smaller datasets will have reduced power to detect a similar treatment which

might lead to a number of erroneous conclusions. In the current study, for age subgroup the cut-off point was age 55 years old. This point was used because age 55 has been used in many earlier studies as the cut-off for younger patients (Julin *et al.,* 2010). Furthermore, the age of 55 years has been used in many earlier studies as the cut-off for eligibility for TKR (Keenan *et al.,* 2012,). For gender subgroup, patients were distributed according to their gender, males or females. Regarding BMI subgroups, the cut-off points were overweight (25–29.9 Kg/$m^2$), obese (30–39.9Kg/$m^2$), and severely obese (≥ 40 Kg/$m^2$) according to the BMI classification of the UK National Health Service (NHS, 2010); this classification is applied in the KSA. Finally, for level of education, patients were divided into educated or uneducated; patients who have secondary school and higher categorised to be educated and who have less than secondary school have lower levels of education (uneducated). Table 6.28 shows subgroups distribution for both groups.

**Table 6-28 subgroup distribution**

| | Age groups | | BMI | | | Gender | | Education level | |
|---|---|---|---|---|---|---|---|---|---|
| | 35-54 | 55-74 | Overweight (25–29.9 Kg/$m^2$) | Obese (30-39.9 Kg/$m^2$) | Morbidity obese (≥40 Kg/$m^2$) | F | M | Educated | Uneducated |
| Active group | 15 | 11 | 3 | 21 | 2 | 16 | 10 | 11 | 15 |
| Control group | 9 | 14 | 4 | 15 | 4 | 15 | 8 | 8 | 15 |

With regard to VAS as a dependent variable, the UAV showed that there was evidence that the active group showed better improvement than the control group after 6 weeks and 6 months of the last treatment session ($p < 0.05$) (Table 6.29). Furthermore, there was evidence that BMI is an influential factor at 6 weeks assessment periods ($p < 0.05$) (Table 6.29), however, due to heterogeneity of patient numbers in the subgroups, it is difficult to make any reliable conclusion.

**Table 6-29 Univariate Analysis of Variance** - (VAS): **95% CI and P-value for main effects in linear model applied separately at each time.**

| | 5 sessions<br>95% CI<br>P-value | 9 sessions<br>95% CI<br>P-value | 6 Weeks<br>95% CI<br>P-value | 6 Months<br>95% CI<br>P-value |
|---|---|---|---|---|
| Treatment Groups | (-2.22 to 0.43)<br>0.18 | (-1.68 to 0.81)<br>0.48 | (-2.11 to 0.05)<br>**0.04*** | (-2.78 to -0.40)<br>**0.010*** |
| Age | (-1.87 to 0. 94)<br>0.51 | (-1.62 to1. 02)<br>0.65 | (-1.88 to 0.30)<br>0.15 | (-1.40 to 1.14)<br>0.85 |
| Gender | (-1.49to 1.71)<br>0.99 | (-1.81 to 1.19)<br>0.68 | (-0.53 to 1.95)<br>0.25 | (-2.15 to 0.73)<br>0.32 |
| BMI ** | (-1.16 to 4.08)<br>0.27<br>(-1.29 to 2.74)<br>0.47 | (-1.63 to 3. 29)<br>0.50<br>(-2.18 to 1.6.9)<br>0.83 | (0.38 to 4.44)<br>**0.02***<br>(-1.15 to 2.17)<br>0.53 | (-1.85 to 2.86)<br>0.67<br>(2.75 to 0.86)<br>0.29 |
| Level of education | (-0.24 to 2.77)<br>0.09 | (-0.52 to 2.32)<br>0.21 | (-1.11 to 1.24)<br>0.91 | (-0.74 to 1. 97)<br>0.37 |

*, $p < 0.05$

**, As BMI has three categories there should be two parameter estimates.

Comparisons were done aginst variables of both groups of the study.

However, the UAV showed that there was no evidence of any interaction between the treatment and the other variables at any time of evaluation (Table 6.30).

**Table 6-30 Univariate Analysis of Variance (interaction)** - (VAS): P values for interaction of treatment with other covariated.

| VAS | 5 sessions P-value | 9 sessions P-value | 6 Weeks P-value | 6 Months P-value |
|---|---|---|---|---|
| Treatment groups * age | 0.59 | 0.82 | 0.55 | 0.68 |
| Treatment groups * gender | 0.97 | 0.58 | 0.37 | 0.47 |
| Treatment groups *BMI | 0.63 | 0.62 | 0.21 | 0.35 |
| Treatment groups * Level of education | 0.20 | 0.20 | 0.96 | 0.37 |

With regard to SKFS as a dependent variable, the UAV showed that there was evidence that the active group showed better improvement than the control group after 6 months of the last treatment session ($p < 0.05$) (Table 6.31), otherwise, there was no evidence of any significant relationship or interaction between the variables ($p > 0.05$) (Tables 6.31 and 6.32).

**Table 6-31: Univariate Analysis of Variance** - (SKFS): **95% CI and P-value for main effects in linear model applied separately at each time.**

| | 5 sessions<br>95% CI<br>P-value | 9 sessions<br>95% CI<br>P-value | 6 Weeks<br>95% CI<br>P-value | 6 Months<br>95% CI<br>P-value |
|---|---|---|---|---|
| Treatment groups | (-16.12 to 6.82)<br>0.42 | (-20.63 to 0.97)<br>0.73 | (-20.22 to 2.38)<br>0.11 | (-23.03 to -2.52)<br>**0.02*** |
| Age | (-23.98 to 0.34)<br>0.06 | (-22.67to 0.23)<br>0.55 | (-21.00 to 2.95)<br>0.14 | (-15.10 to 5.84)<br>0.36 |
| Gender | (-3.60to 24.09)<br>0.14 | (-5.90 to 20.18)<br>0.28 | (-8.53 to 18.75)<br>0.45 | (-17.66 to 7.09)<br>0.39 |
| BMI** | (-32.36 to 12.99)<br>0.39<br>(-21.18 to 13.77)<br>0.67 | (-29.80 to 12.90)<br>0.43<br>(- 17.39 to 15.46)<br>0.91 | (-18.36 to 26.30)<br>0.72<br>(-14.40 to 19.94)<br>0.75 | (-29.50 to 11.02)<br>0.36<br>(-24.48 to 6.70)<br>0.26 |
| Level of education | (-10.39to 15.80)<br>0.68 | (-6.63to 18.03)<br>0.36 | (-10.91 to 14.89)<br>0.76 | (-5.31 to 18.09)<br>0.28 |
| *, $p < 0.05$<br>**, As BMI has three categories there should be two parameter estimates. | | | | |

**Table 6-32 Univariate Analysis of Variance (interaction)** - (SKFS): P values for interaction of treatment with other covariated.

| | 5 sessions<br>P-value | 9 sessions<br>P-value | 6 Weeks<br>P-value | 6 Months<br>P-value |
|---|---|---|---|---|
| Treatment groups * age | 0.20 | 0.16 | 0.41 | 0.50 |
| Treatment groups * gender | 0.43 | 0.74 | 0.86 | 0.50 |
| Treatment groups *BMI | 0.90 | 0.66 | 0.82 | 0.32 |
| Treatment groups * Level of education | 0.87 | 0.63 | 0.89 | 0.66 |

# Chapter 7 Discussion

## 7.1 Introduction

The results of this study showed that the active LLLT applied to specific APs around the knee, in combination with quadriceps strengthening exercises and advice, effectively reduces pain and improves knee joint function, with an improvement in the VAS and SKFS measurements noticed in the treatment group up to the last time point in the study at six months post-treatment compared with the placebo group. The effect of the additional treatment of exercise and advice might also be beneficial to patients with KOA, as demonstrated by the improvements of most outcomes in virtually all patients involved in this study. Of course, there may have been a contribution from the placebo effect and indeed 'trial participation effect' (participants may experience improved clinical outcomes simply by participation in a clinical trial itself), but these would be expected to be equally distributed in both groups.

## 7.2 Changes in the outcome measurements through the study

The primary outcome of the current study was the change in the VAS score for pain during movement. Lee *et al.* (2003) stated that small changes in the VAS may have statistical significance, without clinical meaning. They suggested that a 3 cm mean reduction in VAS represents a clinically relevant difference in pain severity.

In the current study, the within-group analysis showed that OA symptoms had significantly improved in the active laser group at the 5th session of the treatment, as measured by a reduced VAS score for knee pain. Interestingly, this improvement became clinically and statistically significant at the remaining three periods of assessment, respectively (Table 6.3 and Figure 6.1). This implies that there is a residual positive effect of the treatment (active laser, quadriceps exercise, and advice) until six months post-treatment, even though the active treatment had stopped at 3 weeks (9

sessions). The placebo group (placebo laser, quadriceps exercise, and advice) failed to display such effect, although it was also found to reduce the VAS scores statistically (but not clinically) at the 1st 3 follow-up periods. This improvement deteriorated and was not detected at six months, and the differences between the placebo and treatment groups increased (Table 6.3 and Figure 6.1).

The between-groups analysis showed statistically (but not clinically) significant difference in the VAS scores after 6 weeks and after 6 months of the end of treatment in favour of the active laser group (Table 6.13). However, there was no significant clinical difference found between the two groups in the VAS score.

SKFS was the most important secondary assessment tool for the current study. Similar to the VAS, the within-group analysis showed that OA symptoms had significantly improved in both groups at all assessment periods, as measured by a reduction in total SKFS scores and in SKFS subscales (pain, stiffness, physical function, social function, and emotional function) (Table 6.4 to Table 6.9; and Figure 6.2). However, the between-groups comparisons showed that OA symptoms of participants in the active laser group had significantly improved at the last session of the treatment and at the week-6 assessment measured by a reduced SKFS score (Table 6.14).

Regarding subscales of the SKFS, the between-groups analysis showed that patients in the active laser group experienced significant improvement in pain at week 6 and 6-month assessment (Table 6.15), stiffness at the last session and week-6 assessment (Table 6.16), and physical function at week 6 and 6-month assessment (Table 6.17) compared with those in the control group by a reduced SKFS score for knee pain, stiffness, and physical activities. Obviously, this finding supports the previous discussion of the VAS findings.

With respect to social function and emotional function subscales, in spite of the statistically significant difference within both groups (Tables 6.8 and 6.9), the between-groups comparisons showed no difference at any time of assessment (Tables 6.18 and 6.19). This finding could be attributed to the religious background of most of the participants in both groups, who believe that this disease has come from God and that it will not affect them socially or emotionally, according to their answers in this particular section.

ROM, as a secondary assessment tool for the current study, showed a significant improvement at all assessment periods for the participants in the active laser group, whereas this improvement in the control group was only at the 5th and 9th session assessment periods (Table 6.10 and Figure 6.3). Nevertheless, between-groups comparisons showed statistically significant improvement in favour of the active laser group at the 6-month assessment period only (Table 6.20 and Figure 6.3). The previous result was logical because patients in the active laser group and those in the control group recorded relatively acceptable ROM at the baseline assessment with a mean ROM of 128.9° and 129° respectively. The short- and long-term improvements in the ROM and in the other outcomes of the active laser group participants can be attributed to the treatment provided (active laser, quadriceps exercise, and advice).

However, the short-term improvement shown by the participants in the control group could be related to the quadriceps exercise and advice provided, in addition to the placebo effect. Maintained improvement in the ROM and the other outcomes among participants in the active laser group and the relapse among participant in the control group implies that the positive effect of LLLT is sustained at least until 6 months after the treatment ceased.

Previous findings of the sustained positive effect of LLLT are supported by the continued patient satisfaction of participants in the active laser group, even at 6 months after discontinuing the treatment (Table 6.12). A statistically significant difference of patient satisfaction within the control group was seen in all follow-up assessments, except after 6 months (Table 6.12). This could be attributed to the quadriceps exercise and advice provided, in addition to the placebo effect, in that participants might believe they had received a treatment that could improve their situation during that period.

The KC assessment did not indicate a significant change between groups at any assessment period (Table 6.21), even though the within-group analysis showed a significant improvement within the control group at the 9th session and at the 6-months assessment (Table 6.11). This result could be because the majority of participants in both groups had no significant swelling in their joints, or it could be because the LLLT type and/or its parameters used in the current study had no effect on the joint swelling.

In summary, the most significant improvements have been found in the active laser group, compared to the control group, in almost all outcome measurements after 6 months treatment cessation, which suggests that there was a sustained therapeutic effect of active LLLT that was not seen in the placebo group.

## 7.3 Correlation and relationship between variables

In the current study, a correlation analysis has been done to test the degree of association between variables. Pearson correlation coefficients reported in Table 6.23 suggested that age and BMI does not correlate significantly with the changes in the VAS scores through all assessment periods. This was the case regarding the SKFS, although a moderate significant positive correlation was seen at the last treatment session (Table 6.24). A moderate significant negative correlation was noted between BMI and ROM in the control group at baseline, last treatment session, and at week 6 assessment periods (Table 6.25). However, the significant negative correlation was expected to be seen in both groups, because it is logical that ROM increases as BMI decreases, but it was not the case in the active laser group (Table 6.25). A moderate to strong significant positive correlation was noted in both groups between BMI and KC (Table 6.26), which is a logical and expected result.

Nevertheless, in the active group and at the endpoint assessment, there was a strong significant negative correlation between age and patient satisfaction, which implies that older patients might need a special consideration and another dose of the treatment might need to be re-applied earlier than in a younger patient (Table 6.27). Also, in the control group, there was a moderate significant positive correlation between BMI and satisfaction, which could be attributed to the strengthening exercises and advice, which was provided, in addition to the placebo effect. In general, for patients with KOA, the greater the BMI, the more knee pain and activity limitations, therefore, their satisfaction might be increased with a slight improvement more than the others did.

In the current study, data have been analysed to investigate the effects of different variables and their interaction with treatment. In effect, subgroup analyses were undertaken to investigate if the effects of treatment are different across particular groups

of patients by using the UAV test. The result showed that there was no interaction between the variables and treatment at any time evaluation with regard to the VAS (Table 6-29). However, because of the heterogeneity of the number of patients in the subgroups (overweight group= 7, obese group= 36, and morbidly obese group = 6), it is difficult to make a reliable conclusion. However, this might be taken into account in future studies. Regarding the SKFS, the subgroup analysis showed that there was no evidence of any significant relationship or interaction between the variables and treatment (Tables 6-31 and 6-32). This implies that there was no evidence of a differential response to the treatme, regardless of the other variables.

## 7.4 The observed results and the current literature.

Corroborating the findings of Alfredo *et al.* (2011), improvements seen in the active laser group might be attributed to the anti-inflammatory properties of the LLLT applied onto specific points on the articular capsule. Analgesia induced by LLLT resulted in improved exercise performance, and this combination resulted in maintaining benefits up to 6 months, even after laser therapy was discontinued.

Tascioglu *et al.* (2012) reported that several studies show that LLLT has anti-inflammatory, anti-oedema effects, and plays a role in pain reduction without side effects. Although LLLT is clinically used to relieve pain, the mechanism by which it reduces pain is still not clear. However, pain relief can be as an inhibition of nociceptive signals at peripheral nerves. Furthermore, it has also been demonstrated that the LLLT induces analgesia by increasing endorphin and serotonin release (Abrisham *et al.,* 2011; Fulop *et al.,* 2010), see Section (3.8.2) for more details. Nevertheless, this improvement can be attributed to the ability of LLLT to stimulate reparative properties in human cartilage and to improve bone tissue healing (Bouvet-Gerbettaz *et al.,* 2009; de Paula Eduardo *et al.,* 2010; da Rosa *et al.,* 2012).

On the other hand, analgesia sustained among participants in the active laser group can be considered as a result of stimulating specific APs. The five APs used in the current study (ST35, Ex-LE4, ST36, SP9, and SP10) are commonly used in clinical trials of AP in order to treat patients with KOA (Ahsin *et al.,* 2009; Berman *et al.,* 2004; Foster *et al.,* 2007; Taechaarpornkul *et al.,* 2009; Tsang *et al.,* 2007 ). It has been stated that LLLT appears to exert equivalent effects to needle AP, whereas LLLT can act at the skin level through an inhibitory mechanism through a neural blockade. Furthermore, it has been reported that LLLT, when applied to APs, has been shown to be a highly effective therapeutic technique for pain (Silberstein, 2013).

However, in the current study, sustained improvement in the active laser group up to six months after the last treatment session could be attributed to the combined positive effects of LLLT with strengthening exercises and education (advice). Patients with KOA have a significant decrease in knee muscle strength, especially the quadriceps muscle, which increases knee pain; however, there is strong evidence suggesting that exercises can reduce pain and improve function in patients with OA (Conroy *et al.,* 2012; Iwamoto *et al.,* 2011; Pisters *et al.,* 2007). Therefore, exercise is a core recommendation in all international guidelines as a first-line management method for patients suffering KOA (Stemberger and Kerschan-Schindl, 2013).

The average weight of participants in the current study was 86 kg; obese and overweight participants were advised to lose weight, whereas the others were advised to maintain their weight in a normal range. Interestingly, it has been shown that a loss of 5 Kg may be associated with a 50% reduction in the possibility of developing symptomatic KOA, and reduction in the severity of joint pain. In contrast, the risk for KOA is increased by 36% for every 5 Kg of weight gain (Felson, 1996; March and Bagga, 2004; McGoey *et al.,* 1990). Furthermore, it has been reported that for each kilogram of body weight lost, there is a 4 Kg reduction in load on the knee joint per step (Messier *et al.,* 2005).

Patients in the current study were advised not to bend their knees excessively, to wear comfortable shoes, to use an aid or support such as walking stick if necessary, and to avoid activities such as lifting heavy objects while climbing stairs. Additionally, all patients were advised to perform their exercise gently, slowly, and in small amounts and often. Joint protection plays a major role in preventing further damage of the joint structures. By eliminating the influences that can potentially affect or damage the joint components, the development of OA can be prevented or at least slowed down (Michael *et al.,* 2010). Therefore, education and self-help programmes can reduce symptoms and improve QoL in many patients with KOA (Zhang *et al.,* 2009).

Naturally, the fact that all patients in both groups of the current study exercised regularly and were better-educated about their condition played a major role in the improvement seen in participants of both groups. However, the sustained improvement in the active group and the reducing improvement in the control group after 6 weeks and after 6 months from the last treatment session in terms of significant difference found between groups in the primary outcome VAS, SKFS, ROM, and patient satisfaction have many interpretations. First, the combination of the positive effects of strengthening exercises and advice with LLLT is superior to the strengthening exercises and the advice alone. Second, it can be assumed that participants in both groups had stopped the exercises and the advice given. As a result, the positive effect of the strengthening exercise and advice and even the placebo effect deteriorated; however, a positive effect of LLLT on participants in the active group was sustained. Previous interpretations could be supported by the deterioration in patient satisfaction within the control group at the 6-month assessment period in addition to the patient satisfaction being superior in the active laser group compared to the placebo during this period.

Interestingly, the average of the knee ROM of participants in the current study was 129° at baseline evaluation, which was greater than that of similar studies (Alfredo *et al.,*

2011; Gur *et al.,* 2003a; Hegedus *et al.,* 2009) at their post-treatment periods. Therefore, in the current study, no significant improvement was possible between both groups at any time throughout the study, except at the 6-month assessment ($p = 0.046$). This supports what has been previously found by Szabo *et al.* (2000), that Arabians with KOA who follow the Muslim faith have an average ROM of 139.5°, in comparison with non-Arabic patients who are not of Muslim faith, who have an average of 102.8°. Previous findings could be attributed to the lifestyle practiced by Arab and Muslim societies, in which the traditional Arabic way of sitting and the Muslim way of praying force their knees into deep flexion for longer periods during the day (Section 5.5.2).

## 7.5 Comparison between the current study and other studies with similar objectives.

The current RDBCT was conducted to evaluate the efficacy of LLLT applied to five specific APs in combination with exercises and advice on pain, function, and QoL in patients with KOA. Shen *et al.* (2009) conducted a pilot RSBCT to assess the efficacy and safety of two combined types of laser irradiation in patients with KOA when AP Dubi (ST35) is irradiated. Patients were treated by a 650 nm semiconductor laser and 10.6 μ m $CO_2$ laser in a total of 12 sessions, with irradiation time of 20 minutes for each patient in each session. Primary outcome measurement was the WOMAC index and the secondary was the global patient assessment. All patients were evaluated at baseline and week 2.

However, in comparison with the current study, Shen *et al.* (2009) used a different laser device with different parameters for irradiating only one AP and for a longer irradiation time. The current study appears to be more rigorous than the Shen *et al.* (2009) study for many reasons. Shen *et al.* (2009) provided no information about whether the study was powered or not. Furthermore, their study was designed as a single RCT, and the

authors of the study were forced to cancel the 4 week assessment as a result of high a dropout rate. Despite that, both studies showed statistically significant improvement in pain, stiffness, and function of patients in the laser group when compared with the placebo group. Nevertheless, due to the small sample size and the high dropout rate of patients in the placebo group of Shen *et al.* (2009), the authors could not conclude whether the positive result of their study was due to the therapeutic effect or to a placebo effect.

Yurtkuran *et al.* (2007) conducted a RDBCT to investigate the efficacy of LLLT (GaAs infrared laser 904 nm with 10 $mW/cm^2$ power density, 4 mW output power, 0.4 $cm^2$ spot size, 0.48 J dose per session, and 120s treatment time) in patients with KOA when AP SP-9 was irradiated. Similar to the current study, knee exercise was added to the treatment regime. All participants received a total of 10 treatment sessions and were evaluated at baseline, after the treatment, and at the 12th week. The main outcome measures were WOMAC, VAS, 50-foot walking time, KC, and medial tenderness score, and the secondary outcome was the Nottingham Health Profile.

In comparison with the current study, a different laser type was used with different parameters; a lower dose (0.48 J/point) was applied in the Yurtkuran *et al.* (2007) study for longer irradiation time on only one AP. Both studies used VAS and KC among their outcome measures and both added advice and exercise to the treatment program. While the current study showed a statistically significant decrease in VAS scores as a primary outcome of the endpoint assessment (6 months) in favour of the active laser group compared with the placebo group (mean difference = -1.8 and $p < 0.05$), Yurtkuran *et al.* (2007) showed no statistically significant decrease in the VAS at any time of assessment (endpoint, $p = 0.502$). The statistically significant decrease in the VAS scores in the current study could be attributed to the irradiated five APs instead of one AP as in Yurtkuran *et al.* (2007).

However, Yurtkuran *et al.* (2007) found that active treatment was not superior to placebo treatment, except in KC, which was superior in the laser group at the second week. In contrast, this study showed that improvements in the active laser group were statistically superior to those of the placebo laser group in most outcome measures but not in the KC. Corroborating these finding, Hegedus *et al.* (2007) reported that the lack of the effect of LLLT on KC is expected, and it has not been demonstrated with other therapies. However, in the Yurtkuran *et al.* (2007) study, the improvement in the KC could be attributed to the stimulation of AP SP9, which was irradiated for 20 minutes each session for 10 days. In TCM, AP SP9 is a main point for eliminating accumulations of water and moisture, especially in the lower half of the body (Hecker *et al.,* 2008).

Furthermore, the improvement could be attributed to the type of laser and its parameters used in their study, whereas it has been reported that different lasers may have different effectiveness (Tascioglu *et al.,* 2012). According to Azevedo *et al.* (2006), previous studies have suggested that LLLT at energy densities up to 4 J/cm$^2$ has stimulating effects, whereas higher energy fluencies have rather inhibitory characteristics.

Currently, there are two ongoing studies that use laser acupuncture for treating patients with KOA. The first study is being conducted by Hinman *et al.* (2012), which has a two-stage Zelen design RCT to investigate the efficacy of needle and laser acupuncture in patients with chronic knee pain and to evaluate maintenance of effects over the long-term. In comparison with the current study, Hinman *et al.* (2012) is an ongoing trial, so there are no results as yet. In terms of methodology, it is a much bigger trial where authors of the study have potentially better control of the trial design, given the experience of the steering group, however, the nature of their design, such as multi-centric and size of the trial makes it much more difficult to control for flaws in the implementation of the design. Hinman and his colleagues are aware of this and tried to

control by requiring specific training for all participating operators. Whereas, the current study by comparison is small, but also had a robust design and is certainly an improvement in relation to existing literature, in the sense that it is already concluded and provides new relevant data. Furthermore, the current study was controlled for all the variables that proved problematic in previous studies such as Shen *at al.* (2007) and Yurtkuran *et al.* (2007). The single operator design has advantages and disadvantages, for instance, it certainly introduces a consistency of technique that is impossible to obtain with multi-operators. Hinman's design is very complicated and the complication sometime makes it difficult to exclude bias sources, as statistical corrections are limited in their ability to correct practical problems and will in their own right introduce a further bias that is difficult to detect, since the statistical corrections are by necessity based on unproven or untested assumptions. Moreover, primary and secondary outcomes used by Hinman and his colleagues are collected via a self-report questionnaire and mailed back to the investigators, howevere authors did not add any objective measurements to add more support for their result. Despite these criticisms, the Hinman *et al.* (2012) study is still a well-designed trial and will have a longer term assessment; furthermore, interestingly, it is the first study to compare laser acupuncture with needle acupuncture in treating patients with KOA. More details on comparisons between the current study and Hinman *et al.* (2012) are presented in Appendix (XVII).

The other ongoing study was designed by Ress (2012) as a RDBCT to evaluate the effectiveness of laser acupuncture on patients with KOA. Sixty participants are being recruited and randomised into two groups, intervention and placebo. Treatment is being administered 3 times per week for 4 weeks (12 treatments) and the whole treatment time is about 45 minutes. Outcome measures are being administered before and after the 12 treatments and at two months follow-up. According to the study authors so far 30 participants have taken part in this study and preliminary results indicate the use of laser

acupuncture to treat KOA could be positive. However, it is difficult to compare the current study with the Ress (2012) study due to the dearth of available information derived from the study, which is currently only appears to be published as an abstract from the Laser Helsinki 2012 International Congress.

Many other studies have been conducted to investigate the efficacy of LLLT on patients with KOA when applied to different areas, rather than on APs. Alfredo *et al.* (2011) conducted a RDBCT to estimate the effects of LLLT in combination with a programme of exercises on patients with KOA. Although the current study showed a significant difference in VAS at endpoint assessment in active laser over placebo, Alfredo *et al.* (2011) did not (mean difference -0.31, p= 0.120). However, both studies suggest that LLLT when associated with exercises is effective in reducing pain and improving function and activity in patients with KOA.

Hegedus *et al.* (2009) conducted a RDBCT to investigate the effect of LLLT in pain and possible microcirculatory changes in patients with KOA. They used almost identical laser parameters as in the current study, but the dose was 6 J/point compared to the current study of 1.20 J/point. Nevertheless, both studies showed a significant reduction in VAS scores in the active laser group, as compared with the placebo group at the endpoint assessment ($p < 0.05$). Tascioglu *et al.* (2004) conducted a RSBCT to investigate the analgesic efficacy of LLLT in patients with KOA. They suggested that LLLT has no effect on pain in patients with KOA. Almost identical results were found by Bulow *et al.* (1994), who carried out a RDBCT to investigate the effect of LLLT on patients with chronic KOA with periarticular tender points. They failed to find significant differences in any effect variables when comparing an active laser group with a placebo group.

In contrast, a RDBCT done by Gur *et al.* (2003), results showed that applications of LLLT in different doses and duration have not affected results and both therapy regimes were a safe and effective method in treatment of KOA. In a partially RDBCT done by Stelian *et al.* (1992), it was found that LLLT is effective in relieving pain and disability in patients with KOA. However, Trelles *et al.* (1991) conducted a non-randomised and non-controlled study to investigate the efficacy of LLLT in patients with KOA and concluded that this treatment is a safe, effective, and non-invasive alternative to conventional surgical and medical treatment modalities for patients with degenerative KOA.

Nevertheless, studies done by Shen *et al.* (2009) and Yurtkuran *et al.* (2007) used only one AP irradiated by LLLT, in the current study, five APs were irradiated, making it more comparable to clinical trials involving conventional acupuncture. Ahsin *et al.* (2009) carried out a RSBCT to investigate the effect of EA on pain intensity and plasma levels of endorphin and cortisol. They stimulated six APs, three of which were used in the current study (ST35, ST36, and SP10). Their study suggests that EA is effective for relieving pain, stiffness and functional disability with an increase in plasma-endorphin, and a decrease in plasma cortisol, as compared with sham acupuncture in patients with primary KOA. However, the reduction in the VAS pain score showed a similar trend with the sham group, showing no reduction in median score.

Taechaarpornkul *et al.* (2009) conducted a comparative randomised trial to compare the effectiveness of six and two APs in the treatment of KOA using EA. Five of these six APs were used in the current study (ST35, EX-LE4, ST36, SP9, and SP10). The result of their study pointed out that acupuncture at both six and two APs was associated with a significant improvement; however, there was a non-statistically significant improvement in pain in subjects who received both two and six APs. Therefore, the

authors of the study suggested that EA applied to two local points may be sufficient to treat KOA.

Jubb *et al.* (2008) in their RCT to compare electro acupuncture and manual acupuncture with sham acupuncture, all five APs used in the current study were among the ten APs that were irradiated by Jubb and his team. The result of their study showed that acupuncture is significantly superior to non-penetrating sham acupuncture for patients with KOA. A multicentre RCT was carried out by Foster *et al.* (2007) to investigate the benefit of adding acupuncture to an exercise and advice program for pain reduction in patients with KOA in older adults. This study is identical to the current study in that all participants received an exercise and advice program. The five APs used in the current study (ST35, EX-LE4, ST36, SP9, and SP10) were stimulated in addition to another ten APs irradiated by Foster and his colleagues. However, in contrast to the current study results, they clarified that the addition of acupuncture to a course of advice and exercise for KOA provided no additional improvement in pain scores.

Berman *et al.* (2004) conducted an RCT to determine the efficacy of true acupuncture compared with sham acupuncture or education in patients with KOA. Of 9 APs used in their study, 4 APs ST35, Xiyan, ST36, and SP9 of the current study were used. The authors concluded that acupuncture seems to provide improvement in function and pain relief as an adjunctive therapy for KOA, in comparison with credible sham acupuncture and education control groups. A prospective controlled trial was done by Tillu *et al.* (2002) comparing acupuncture with no treatment in patients with advanced KOA awaiting TKR. The APs SP9, SP10, and ST36 used in the current study were among the five APs used in their study. The result showed that the acupuncture group improved in all parameters, whereas the control group deteriorated.

Finally, Suarez-Almazor *et al.* (2010) conducted an RCT in patients with KOA to compare the efficacy of traditional acupuncture with sham acupuncture. Only one AP (SP9) of those used in the current study was among APs used in the study by Suarez-Almazor and his colleagues. Their results showed that traditional acupuncture was not superior to sham acupuncture, and the needling of meridian points was no more effective than the use of sham points.

## 7.6 Problems and limitations of the study

During the planning stage of this study, there was difficulty in finding published studies related to the use of LLLT in treating KOA. Furthermore, studies concerning laser acupuncture are rare. To the best knowledge of the author, to date, only two studies have been published for testing the efficacy of LLLT when applied on APs in patients with KOA; moreover, only one AP has been stimulated in each study (Shen *et al.,* 2009; Yurtkuran *et al.,* 2007). Despite the dearth of published studies on the use of laser therapy in KOA, many problems and limitations were found, including the lack of standard protocols for inclusion and exclusion criteria. In addition, LLLT studies have been criticised because the laser devices, experimental designs, parameters, and techniques used in the literature are highly variable. Therefore, it is important for one to be careful when reviewing and comparing these studies.

VAS as a primary outcome for the current study has been shown to be influenced by many factors, including age, mental condition, impaired sensation, and the subject's psychological condition (Lu *et al.,* 2010). Furthermore, the SKFS used as a secondary outcome for the current study, such as other pain and functional outcome measurement scales used in similar studies, is influenced by some diseases other than KOA. Older patients with KOA frequently present several co-morbidities, including low back pain, fibromyalgia, rheumatoid arthritis, depression, and fatigue. Therefore, care should be taken when using such assessment tools to assess the efficacy of treatment. To fill this gap, objective and precise assessment tools are necessary, e.g. three-dimensional gait analysis (Lu *et al.,* 2010).

The use of scales, such as VAS and SKFS, in their concept of evaluation, is still new to Saudi patients, who may be influenced greatly by educational level, as the illiteracy rate

among the participants in the current study is relatively high. It has been reported that highly educated patients show a better outcome and response (Hmamouchi *et al.,* 2012). Another limitation, which has already been found in most similar studies, is that the study samples included more female than male participants; for example, in the current study, 63.5% of the participants were female. Therefore, representativeness of the sample for both genders may be influenced.

An additional limitation is that more than 61% of the participants in the current study were uneducated. Educated patients are expected to have the ability to apply the instruction in a better manner and to express their feedback in a better way than uneducated patients can. Especially in subjective assessment scales, such as VAS and SKFS, information obtained from educated patients is likely to be more accurate and hence could be an important factor in determining the outcome of a study.

# Chapter 8 Conclusion

## 8.1 Conclusion

LLLT is one of the most recent pain management modalities in the field of physiotherapy. Recent studies have clearly shown that laser light can be successfully used as an alternative to metal needles (Laser acupuncture) for effective AP treatment. Furthermore, LLLT is safer and it requires less time than needle AP; hence patients can avoid the pain and psychological fear associated with traditional AP.

This study appears to be the first RDBCT to investigate the efficacy of LLLT when applied to more than one AP in patients with KOA: five APs were irradiated. Furthermore, it is the first RDBCT study conducted in the Arabic world using LLLT for treating patients with KOA and the first study to use the SKFS as an outcome measure for KOA.

A reasonable sample-size and follow-up period was employed in the current study, in comparison with similar studies of LLLT for treating KOA. The results of our study demonstrated that short-period application of LLLT (three sessions weekly for three weeks, for a total of nine sessions) on specific APs on patients with KOA, in conjunction with exercise and advice, has a beneficial positive effect on pain reduction and improvement in knee joint function, with an improvement in all outcomes except KC Despite the current study showed that there was statistically significant difference (but not clinically difference) between groups of the study, both groups of the study showed relative improvement over the study period, but the patients receiving active laser acupuncture had a significantly greater improvement at the end point evaluation. Although the current study indicated that active laser is superior to the placebo, the placebo effect is also clearly beneficial to patients with KOA, as demonstrated by the improvements of most outcomes in virtually all patients involved in this study.

According to Ernst (1994) no clinical research can be without flaws. Therefore, despite the aforementioned limitations and problems encountered during the completion of the current thesis (Section 7.6), it has provided evidence to add to the scientific basis around the use of LLLT in treating patients with KOA. The findings of this study are important, especially for those patients who seek non-pharmacological analgesia without side effects and for patients who are not candidates for, or refuse, surgery. Additionally, the results of the study showed that LLLT might make a contribution as an adjunct to other forms of interventions for KOA.

Because of the lack of a standard regimen for treating patients with KOA compared to other physiotherapy interventions, which usually require a longer time, it is fair to say that LLLT is time-and-effort saving for both patients and practitioners. Therefore, LLLT can help in minimising the long waiting lists for patients with KOA and give them an equal chance for receiving an appropriate treatment. The greater pain relief and the improvement in the QoL obtained from LLLT might encourage patients to practise their strengthening exercises with less discomfort and less pain and to become more mobile.

## 8.2 Summary and Implications for Future Research

This study appears to be the first RDBCT to investigate the efficacy of LLLT when applied to more than one AP in patients with KOA. It is the first RDBCT conducted in the Arabic world using LLLT for treating patients with KOA and the first study to use the SKFS as an outcome measure for KOA. The results of this study demonstrate that short-period application of LLLT (GaAlAs infrared LLLT at 830nm wavelengths with a continuous mode, delivering an energy density of 4 J/cm$^2$, with 40 s of irradiation time and a dose of 1.20 J/point per session repeated 3 times a week for 3 weeks) on specific APs in conjunction with exercise, education, and advice are effective in reducing pain

and improving the QoL in patients with KOA. However, the results of this study support LLLT, at the parameters used in the trial, as an important adjunct intervention in the treatment of KOA and possibly for other joints. This modality may be especially relevant for patients who do not respond to medical therapy, for whom other physical modalities are contraindicated, those who suffer adverse side effects of drug therapy, or those who are not candidates for surgery.

As the current study is the first study that used more than one AP for testing the efficacy of LLL in treating KOA, it provides a model for further research. Further well-designed RCTs with longer term findings are required, not only to establish the efficacy of LLLT applied to APs but also to identify important factors including wavelength, treatment duration, dosage, and site of application that significantly increase the heterogeneity of the literature and thus dilute the applicability of the results. In addition, further RDBCTs are needed to investigate a positive effective of LLLT on APs, if any, as a result of stimulating APs directly or as a result of biological effect from surrounding tissues or both. Further studies are required to stimulate the same and/or different APs related to the KOA according to acupuncture regimen, in order to provide scientific evidence about its prospective efficacy.

Laser acupuncture seems to work well when added to an exercise and advice regimen. For more scientific evidence, there is a need for future RCTs to compare LLLT when applied to APs with commonly used non-pharmacological or even pharmacological agents. As aforementioned, the VAS, the primary measurement tool of the current study, in addition to the SKFS, the secondary measurement tool, are subjective tools, which are influenced by many factors, which have been mentioned earlier. Further studies using objective and precise assessment tools are necessary; for example, three-dimensional gait analysis and/or MRI. Furthermore, VAS and SKFS may be influenced greatly by the educational level of the patient; the uneducated patients and the illiteracy

rate among the participants in the current study were relatively high. Therefore, the effect of the educational level on responses may need further study, especially in communities with diverse educational levels.

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# APPENDICES

# APPENDIX I: Search strategy

**Keywords for Search Strategy**

| **Databases searched*** | **Osteoarthritis** | **Low-Level Laser Therapy** | **Acupuncture** |
|---|---|---|---|
| AMED, Biosis, Cinahl, Cochrane Library, Embase, Google Scholar, Medline, NHS Library, Pub Med, Scirus, Scopus, University of Dundee Library catalogue, Web of the Knowledge and Zetoc, The Physiotherapy Evidence Database (PEDro). | Osteoarthritis, Osteoarthritis of knee. OA Knee, Knee OA, Osteoarthrosis, Osteoarthritis AND knee, Osteoarthritis OR knee, Degenerative changes, Knee pain. | Low-Level Laser Therapy (LLLT), Low Energy Laser Therapy (LELT), Low-Intensity Laser Therapy (LILT), Low Energy Photon Therapy (LEPT), Diode laser therapy, Infrared laser therapy, Laser therapy, Light therapy, Soft laser therapy, Cold laser therapy, Visible laser therapy, Semiconductor, Bio-stimulation, Photobiostimulation, Photobioactivation, Photobiomodulation, Phototherapy, Gallium-Aluminium-Arsenide (GaAlAs), Gallium-Arsenide (GaAs), 830 nm, 904 nm. | Acupuncture treatment, Acupuncture for knee joint, Traditional Chinese Medicine (TCM) |
| *, restricted to English language papers | | | |

# APPENDIX II (A): Patient Information Sheet (English version)

**The efficacy of low-level laser therapy applied at acupuncture points in knee osteoarthritis: a randomised double-blind controlled trial**

**Introduction:**

Osteoarthritis of the knee is a common disorder in our community which is usually associated with pain, swelling and stiffness of the knee joint. This study is designed to evaluate the effectiveness of laser therapy when applied on chosen acupuncture points in relieving the pain caused by Osteoarthritis of the knee. Laser therapy is widely used as a medical treatment modality. It is considered to be non-invasive, painless and safe. We are doing a study to investigate the effectiveness of laser therapy when applied to specific acupuncture points at the knee joint in patients with knee Osteoarthritis.

**Methods of the study:**

The study will be conducted in a double-blind fashion. Patients and investigator will be unaware of which treatment the patients received, known only to the research assistant.

In this study, participants will be randomly assigned to either active or placebo laser group based on a sequence of computer generated random numbers. If you wish to participate in the study you will receive a standard physiotherapy assessment of your knee to ensure you are suitable for the study. If you are fit, you will be allocated to one of two groups. That means you will have an equal chance of being included in either the laser group (you will receive active laser + knee exercises and home instructions) or control group (you will receive placebo laser + knee exercises and home instructions).

The laser machine that will be used in this study for both active and placebo groups is the same machine. The placebo emitter is like the active emitter in appearance, but is

inactive (both produce red light); no heat or vibration is detectable from either the active or placebo laser.

You will be asked to record your level of pain and functional disability on standard questionnaires before the first session and after the last one. You will be required to attend physiotherapy department three times weekly for three weeks.

If the participants in the laser group show an increased benefit all the participants will be receiving a laser treatment later on, otherwise a standard physiotherapy treatment will be given.

**Treatment:**

Laser treatment will be applied to chosen acupuncture points in your lower limb by an experienced physiotherapist in laser treatment. 15 minutes for each session are required to have this treatment three times a week for 3 weeks (9 treatment sessions). In addition, 30 minutes are required to be added to the assessment sessions (baseline, at the 5th session, at the 9 th (last) session, 6 weeks and 6 months after the last session).

**Risk from participating in the study:**

Laser therapy used in physiotherapy is usually safe and non-invasive treatment. You will never feel any heat, but you will see a red light. The only possible risk when there is direct laser on your eyes. So, you and the physiotherapist will be provided with special goggles to provide full protection. Also, laser therapy is contraindicated in some cases such as patients with active carcinoma. Laser therapy should be avoided on areas of haemorrhage. Treatment of infected tissue, especially infected open wounds should be avoided as the laser may stimulate the bacteria. Care must be taken for patients with a history of photosensitivity (adverse reactions to sunlight). Direct irradiation over the

pregnant uterus should be avoided as well. So, if you have any of the previous cases, please don't hesitate to inform the researcher.

**Benefits from participating in the study:**

Laser therapy has been shown in some previous studies to be a successful treatment in relieving the pain of Osteoarthritis. The information gathered from this study will help to increase our knowledge of the effectiveness of laser therapy in treating patients suffering from knee pain as a result of Osteoarthritis like yourself and the others. At the end of the study if you have not shown any improvement you will receive the appropriate treatment.

**Inability to participate in the study:**

Participating in this study is voluntary. So, if you do not wish to participate in the study, your normal (standard) treatment will be given to you in the normal way. If you take part, but later you change your mind, at any time you can withdraw from the trial and there is no need to give any explanation and you will be treated in the normal way.

**Confidentially:**

Any information or results that may be gathered from you will be kept confidential. Records will be referred to you as a number rather than name. So, no one can link your results.

*If you need any query about this study, please don't hesitate to contact:*

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Security Forces Hospital
Physiotherapy department
Tel/ 01 4754561
Mobile: 0555487703
E-mail: joud55@yahoo.com

# APPENDIX II (B): Patient Information Sheet (Arabic version)

**معلومات تهم المريض حول الدراسة**

**عنوان الدراسة: استخدام الليزر لعلاج مرضى روماتيزم الركبة عند تسليطه على نقاط مختارة من نقاط الوخز بالإبر الصينية**

**مقدمة:**

روماتيزم الركبة هو اضطراب شائع في مجتمعنا الذي يرتبط عادة بألم وتورم وتيبس في مفصل الركبة. تم تصميم هذه الدراسة لتقييم فعالية العلاج بالليزر عند تطبيقه على نقاط مختارة من نقاط الوخز بالإبر الصينية في تخفيف الألم الناجم عن التهاب في عظام الركبة. ويستخدم العلاج بالليزر على نطاق واسع كعلاج طبي. وهو يعتبر علاج غير مؤلم وآمن.

نحن بصدد إجراء دراسة للتحقق من فعالية العلاج بالليزر عند تسليطه على نقاط مختارة ومحدده من نقاط الوخز بالإبر الصينية على وحول مفصل الركبة للمرضى الذين يعانون من التهاب مفاصل الركبة.

**طرق الدراسة:**

سوف يتم توزيع المشاركين في هذه الدراسة عشوائيا إلى مجموعتين وذلك بواسطة الكمبيوتر. المجموعة الأولى سوف تعالج بواسطة ليزر نشط بينما المجموعة الثانية سوف تعالج بواسطة ليزر غير نشط. ستجرى هذه الدراسة في ظروف خاصة بحيث لن يكون لدى المريض والباحث (أخصائي العلاج الطبيعي ) علم مسبق بنوعية العلاج المستخدم، فقط مساعد الباحث هو من يعرف نوعية العلاج المقدم للمريض.

إذا كنت ترغب في المشاركة في هذه الدراسة فانه سوف يتم تقييمك بواسطة الباحث الرئيس (أخصائي العلاج الطبيعي) لهذه الدراسة للتأكد من أنك مناسب لإجراء الدراسة. إذا كنت مناسباً ،سيتم توزيعك عشوائياً إلى واحدة من المجموعتين السابقتين . وهذا يعني أنه سيكون لديك فرصة متساوية ليتم ضمك ضمن مجموعة الليزر النشط أو إلى مجموعة الليزر غير النشط .

جهاز الليزر الذي سوف يستخدم في هذه الدراسة لكلا المجموعتين هو نفس الجهاز. باعث الليزر غير نشط هو نفس باعث الليزر النشط ولكن الجهاز في هذه الأثناء سوف يكون في وضع السكون. علما بان باعث الليزر في حالة السكون وفي حالة الوضع النشط يبعث لونا أحمرا ولكنه لا يبعث حرارة أو صوتا أو اهتزازا.

سوف يطلب منك أن تسجل مستوى الألم والعجز الوظيفي الذي تعاني منه وذلك من خلال تعبئة استبيانات معيارية مباشرة قبل الجلسة الأولى من العلاج وبعد الجلسة الخامسة ثم بعد الجلسة التاسعة والأخيرة ثم سوف تعطى موعدا للمتابعة بعد أربعة أسابيع حيث سوف يطلب منك أيضا تعبئة نفس الاستبيانات وبنفس الطريقة السابقة. ستكون هناك حاجة لحضورك قسم العلاج الطبيعي ثلاث مرات أسبوعيا لمدة ثلاثة أسابيع.

إذا أضهر المشاركون في مجموعة الليزر النشط تحسنا قياسيا ملحوظا يفوق المشاركين في مجموعة الليزرغير نشط فانه سوف يتم علاج هؤلاء بالليزر النشط بنفس الطريقة وبنفس عدد الجلسات. وإذا كانت النتائج غير ذلك فانه سيتم علاج الجميع بالطرق الفيزيائية الأخرى المتوفرة في قسم العلاج الطبيعي.

**العلاج:**

سيتم وضع باعث الليزر على خمس نقاط موجودة على مفصل الركبة المصابة لديك وحولها لمدة دقيقة لكل نقطة، وسوف يقوم بالعلاج أخصائي علاج طبيعي ذو خبرة بالعلاج بالليزر. خمس عشر دقيقة إلى عشرين دقيقة هي مدة الجلسة العلاجية الواحدة وتشمل العلاج بالليزر وتمارين التقوية والتعليمات والنصائح، أما جلسات التقييم والعلاج فقد تستغرق خمسة واربعون دقيقة ( مباشرة قبل أول جلسة علاج، مباشرة قبل الجلسة الخامسة، مباشرة قبل الجلسة الاخيرة (التاسعة)، ثم بعد ستة اسابيع وبعد ستة أشهر من اخر جلسة علاجية).هذا يتطلب منك الحضور إلى قسم العلاج الطبيعي ثلاث مرات في الأسبوع لمدة ٣ أسابيع (٩جلسات)

**الأخطار والإضرار المحتملة من المشاركة في هذه الدراسة:**

العلاج بالليزر المستخدم في العلاج الطبيعي عادة ما يكون آمن وغير مؤذ. انك لن تشعر بأي حرارة ولكن سترى ضوء أحمر. الخطر الوحيد الممكن عندما يسلط ضوء الليزر مباشرة على عينيك. لذلك فان المريض وأخصائي العلاج الطبيعي سوف يضعون نظارات خاصة على أعينهم لتوفير الحماية الكاملة. أيضا، يمنع استخدام العلاج بالليزر في بعض الحالات مثل مرضى السرطانات النشطة. كذلك يجب تجنب العلاج بالليزر على مناطق النزف وخاصة الجروح المفتوحة والملوثة لأن الليزر يمكن أن يحفز عمل البكتيريا. ويجب توخي الحذر بالنسبة للمرضى الذين لديهم تاريخ من الحساسية من الضوء (ردود الفعل السلبية لأشعة الشمس). وينبغي تجنب الإشعاع المباشر على رحم المرأة الحامل. لذا، إذا كان لديك أي من الحالات السابقة، من فضلك لا تتردد في إبلاغ الباحث.

**فوائد المشاركة في الدراسة:**

بينت بعض الدراسات السابقة أن العلاج بالليزر يعتبر علاجا ناجحا في تخفيف آلام التهاب المفاصل. إن المعلومات التي سيتم جمعها من هذه الدراسة سوف تساعد على زيادة معرفتنا لفعالية العلاج بالليزر في علاج المرضى الذين

يعانون من آلام في الركبة نتيجة لالتهاب عظام المفاصل مثل ما حدث معك ومثل مايحدث مع الآخرين. في نهاية الدراسة إذا لم يظهر لديك أي تحسن سوف تتلقى طرقا" أخرى من العلاج متوفرة في قسم العلاج الطبيعي.

**عدم القدرة على المشاركة في الدراسة:**

المشاركة في هذه الدراسة هو طوعي. لذا، إذا كنت لا ترغب في المشاركة في الدراسة، سوف يتم التعامل معك بالطريقة المتبعة في الوضع الطبيعي. إذا شاركت في الدراسة ثم غيرت رأيك في وقت لاحق وأردت الانسحاب فلك الحق في ذلك في أي وقت تشاء دون الحاجة لإعطاء أي تفسير أو تبرير، وسيتم التعامل معك بعد ذلك بالطريقة العادية المتبعة مع المرضى الاخرين.

**السرية:**

سيتم الحفاظ على كافة المعلومات أو النتائج التي تم جمعها عنكم بسرية تامة. وسوف تسجل الوثائق الخاصة بها كرقم بدلا من اسم. لذا، لا يمكن لأحد الاطلاع أو الاستفادة من النتائج والمعلومات.

*إذا كنت بحاجة إلى أي استفسار عن هذه الدراسة، من فضلك لا تتردد في الاتصال ب:*

الباحث: **عبدا لله الرشود**

مستشفى قوى الأمن
قسم العلاج الطبيعي
جوال : ٠٥٥٥٤٨٧٧٠٣
بريد الكترونيjoud :55@yahoo.com

# APPENDIX III (A): Consent form (English version)

I,……....., freely and voluntarily agree to participate in this research study that conducted at Security Forces Hospital in Physiotherapy department. I understand that I am free to withdraw from the study at any time I wish and there is no need to give any explanation, then I will be treated in the normal way. I further understand that my confidentiality will be preserved.

I have read and understood the information sheet given to me and all questions have been answered to my complete satisfaction.

Signature …… Date……

Participant Name ……. Phone No. ……

**For investigator use:**

I confirm that I have explained the clinical trial and supplied the participant with an information sheet, which, in my opinion, is easy to read and understand by the participant.

Investigator Name…… Date……..

Signature: ……

# APPENDIX III (B): Consent form (Arabic version)

**(نموذج موافقة)**

نعم أنا.....، بحرية وطواعية أوافق على المشاركة في هذه الدراسة التي سوف تقام في مستشفى قوى الأمن بالرياض( قسم العلاج الطبيعي). أفهمت بأنني حر في الانسحاب من الدراسة في أي وقت خلال الدراسة وليس هناك حاجة لإعطاء أي تفسير أو مبرر، ومن ثم سيتم التعامل معي بالطرق العادية المتبعة لدى القسم. كذلك أفهمت بأنه سوف يتم التعامل بالمعلومات الخاصة بي بسرية تامة.

لقد قرأت وفهمت ورقة المعلومات التي أعطيت لي ولقد تمت الإجابة على جميع أسئلتي بالكامل.

الاسم ..... تاريخ.....

التوقيع ..... رقم الهاتف.....

**لاستخدام الباحث:**

أؤكد بأنني أوضحت التجارب السريرية وتزويد المشاركين بورقة المعلومات، والتي في رأيي أنه من السهل قراءتها وفهمها من قبل المشاركين.

الاسم..... التاريخ.....

التوقيع.....:

# APPENDIX IV: Ethical approval

KINGDOM OF SAUDI ARABIA
MINISTRY OF INTERIOR
General Administration for Medical Services
SECURITY FORCES HOSPITAL PROGRAM

المملكة العربية السعودية
وزارة الداخلية
الإدارة العامة للخدمات الطبية
برنامج مستشفى قوى الأمن

**MEMORANDUM**

Date: 08 March 2010

To: **Mr. Abdullah Al-Rashoud**
Senior Physiotherapist, Physiotherapy Department

From: **Prof. Riad A. Sulimani**
Chairman, Research Committee

Subject: **Research Approval**

Following the meeting of the Research Committee on **Sunday 07 March 2010,** I am pleased to inform you that your research proposal, titled "*The Efficacy of Low Level Laser Therapy in The Treatment of Knee Osteoarthritis*". was approved without any condition ,

Thank you and best regards.

Cc:
- Research File

# APPENDIX V: CONSORT

Checklist of Items for Reporting Trials of Non-pharmacologic Treatments

| Section | Item | Standard CONSORT Description | Extension for Non-pharmacologic Trials |
|---|---|---|---|
| **Title and abstract** | 1 | How participants were allocated to interventions (e.g., "random allocation," "randomised," or "randomly assigned") | In the abstract, description of the experimental treatment, comparator, care providers, centres, and blinding status |
| **Introduction** | | | |
| Background | 2 | Scientific background and explanation of rationale | |
| **Methods** | | | |
| Participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected | When applicable, eligibility criteria for centres and those performing the interventions |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered | Precise details of both the experimental treatment and comparator |
| | 4A | | Description of the different components of the interventions and, when applicable, descriptions of the procedure for tailoring the interventions to individual participants |
| | 4B | | Details of how the interventions were standardized |
| | 4C | | Details of how adherence of care providers with the protocol was assessed or enhanced |
| Objectives | 5 | Specific objectives and hypotheses | |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors) | |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules | When applicable, details of whether and how the clustering by care providers or centres was addressed |
| Randomisation–sequence generation | 8 | Method used to generate the random allocation sequence, including details of any restriction (e.g., blocking, stratification) | When applicable, how care providers were allocated to each trial group |
| Allocation concealment | 9 | Method used to implement the random allocation sequence (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned | |
| Implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups | |

| | | | |
|---|---|---|---|
| Blinding (masking) | 11A | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment | Whether or not those administering co-interventions were blinded to group assignment |
| | 11B | | If blinded, method of blinding and description of the similarity of interventions† |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome (s); methods for additional analyses, such as subgroup analyses and adjusted analyses | When applicable, details of whether and how the clustering by care providers or centres was addressed |
| **Results** | | | |
| Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended) ---specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome; describe deviations from study as planned, together with reasons | The number of care providers or centres performing the intervention in each group and the number of patients treated by each care provider or in each centre |
| Implementation of intervention† | New item | | Details of the experimental treatment and comparator as they were implemented |
| Recruitment | 14 | Dates defining the periods of recruitment and follow-up | |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group | When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centres (volume) in each group |
| Numbers analysed | 16 | Number of participants (denominator) in each group included in each analysis and whether analysis was by "intention-to-treat"; state the results in absolute numbers when feasible (e.g., 10/20, not 50%) | |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (e.g., 95% confidence interval) | |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory | |
| Adverse events | 19 | All important adverse events or side effects in each intervention group | |
| **Discussion** | | | |
| Interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision, and the dangers associated with multiplicity of analyses and outcomes | In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centres in each group |

| | | | |
|---|---|---|---|
| Generalizability | 21 | Generalizability (external validity) of the trial findings | Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centres involved in the trial |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence | |

# APPENDIX VI: Randomisation table

| Groups<br>A: Active; C: control | Random blocks | Randomisation numbers |
|---|---|---|
| A | 1 | 0.07 |
| A | 1 | 0.09 |
| C | 1 | 0.15 |
| C | 1 | 0.19 |
| C | 1 | 0.23 |
| A | 1 | 0.31 |
| A | 1 | 0.42 |
| A | 1 | 0.45 |
| C | 1 | 0.59 |
| C | 1 | 0.68 |
| C | 2 | 0.02 |
| A | 2 | 0.31 |
| C | 2 | 0.41 |
| A | 2 | 0.42 |
| A | 2 | 0.48 |
| A | 2 | 0.58 |
| C | 2 | 0.69 |
| C | 2 | 0.77 |
| C | 2 | 0.78 |
| A | 2 | 0.92 |
| C | 3 | 0.01 |
| C | 3 | 0.09 |
| A | 3 | 0.11 |
| C | 3 | 0.19 |
| A | 3 | 0.43 |
| C | 3 | 0.44 |
| A | 3 | 0.51 |
| A | 3 | 0.66 |
| A | 3 | 0.91 |
| C | 3 | 0.93 |
| C | 4 | 0.12 |
| C | 4 | 0.32 |
| A | 4 | 0.36 |
| C | 4 | 0.46 |

| | | |
|---|---|---|
| A | 4 | 0.51 |
| C | 4 | 0.53 |
| A | 4 | 0.55 |
| C | 4 | 0.55 |
| A | 4 | 0.62 |
| A | 4 | 0.87 |
| A | 5 | 0.04 |
| A | 5 | 0.31 |
| C | 5 | 0.36 |
| A | 5 | 0.41 |
| C | 5 | 0.42 |
| A | 5 | 0.48 |
| A | 5 | 0.53 |
| C | 5 | 0.79 |
| C | 5 | 0.84 |
| C | 5 | 0.84 |
| A | 6 | 0.12 |
| C | 6 | 0.15 |
| A | 6 | 0.2 |
| A | 6 | 0.37 |
| A | 6 | 0.42 |
| A | 6 | 0.43 |
| C | 6 | 0.51 |
| C | 6 | 0.55 |
| C | 6 | 0.77 |
| C | 6 | 0.88 |
| A | 7 | 0.23 |
| C | 7 | 0.31 |
| C | 7 | 0.41 |
| A | 7 | 0.41 |
| A | 7 | 0.45 |
| A | 7 | 0.49 |
| C | 7 | 0.55 |
| C | 7 | 0.72 |
| A | 7 | 0.77 |
| C | 7 | 0.81 |
| A | 8 | 0.05 |
| A | 8 | 0.24 |

| | | |
|---|---|---|
| C | 8 | 0.26 |
| C | 8 | 0.26 |
| C | 8 | 0.29 |
| C | 8 | 0.39 |
| C | 8 | 0.42 |
| A | 8 | 0.73 |
| A | 8 | 0.87 |
| A | 8 | 0.91 |
| C | 9 | 0.22 |
| A | 9 | 0.22 |
| C | 9 | 0.31 |
| C | 9 | 0.4 |
| C | 9 | 0.51 |
| A | 9 | 0.52 |
| A | 9 | 0.61 |
| A | 9 | 0.8 |
| A | 9 | 0.81 |
| C | 9 | 0.93 |
| C | 10 | 0.08 |
| A | 10 | 0.1 |
| A | 10 | 0.11 |
| C | 10 | 0.17 |
| A | 10 | 0.25 |
| A | 10 | 0.65 |
| A | 10 | 0.68 |
| C | 10 | 0.73 |
| C | 10 | 0.74 |
| C | 10 | 0.85 |

# APPENDIX VII: Visual analogue scale (Arabic version)

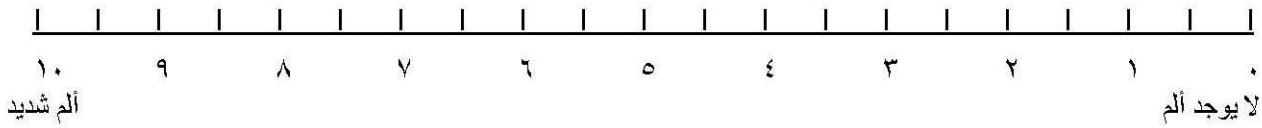
**مقياس مقدار الألم**

Patient No.: .....  Patient Name:.....

أمامك خط مستقيم طوله ١٠ سنتميتر،

(. سم) يعني أنه لايوجد ألم نهائياَ، بينما (١٠سم) يعني أنه يوجد لديك ألم شديد غير محتمل.

**ما هو مقدار الألم الذي تعاني منه في المتوسط بسبب الركبة خلال الفترة الماضية؟**




(Adapted from http://www.britishpainsociety.org/pain_scales_ara.pdf)

SKFS APPENDIX VIII (A) (English version)

| | D | D | M | M | Y | Y |
|---|---|---|---|---|---|---|
| Today Date | | | | | | |

**The Saudi Knee Function Scale**
**A Knee Osteoarthritis Index**

**Instructions**

In each of the five sections in the following questionnaire you will be asked to rate the amount of Pain, Stiffness (slowness or limitation of movement), Difficulty, and Social and Emotional dysfunction, on a scale as follows:


1. If you choose '0' the face on the left hand side then you are indicating that you have no pain
2. If you choose '4' the face on the right hand side then you are indicating that you have extreme pain.

The further to the left you go the less pain, stiffness, difficulty, or dysfunction you are experiencing, and the further to the right the more pain, stiffness, difficulty, or dysfunction you are experiencing.

**A. Pain**

Please indicate the amount of pain experienced in your knee with the following activities over the last three days:

| | | | | | |
|---|---|---|---|---|---|
| 1. At night disturbing sleep, or at rest during the day | 0 | 1 | 2 | 3 | 4 |
| 2. Getting on or off the floor | 0 | 1 | 2 | 3 | 4 |
| 3. Getting on or off a (regular ) chair | 0 | 1 | 2 | 3 | 4 |
| 4. Walking on a flat surface ( short distance approx. 50m) | 0 | 1 | 2 | 3 | 4 |
| 5. Going up and down the stairs (one flight) | 0 | 1 | 2 | 3 | 4 |
| 6. Standing in prayers (or short time < 5 min | 0 | 1 | 2 | 3 | 4 |
| 7. Bowing, prostrating, or sitting in prayers | 0 | 1 | 2 | 3 | 4 |
| 8. Squatting (like when using an Arabic toilet) | 0 | 1 | 2 | 3 | 4 |

**B. Stiffness**

In the following questions you are asked to rate the amount of stiffness (slowness & limitation in movement, not pain) you are experiencing at the knee over the last three days:

| | | | | | |
|---|---|---|---|---|---|
| 1. How severe is your stiffness after first waking in the morning | 0 | 1 | 2 | 3 | 4 |
| 2. How severe is your stiffness after prolonged sitting on the floor or on a chair | 0 | 1 | 2 | 3 | 4 |

**C. Physical Function**

Please indicate the degree of difficulty you are having because of your knee with the following activities over the last three days:

| | | | | | |
|---|---|---|---|---|---|
| 1. Walking on a flat surface | 0 | 1 | 2 | 3 | 4 |
| 2. Getting on or off the floor | 0 | 1 | 2 | 3 | 4 |
| 3. Getting on or off a (regular) chair | 0 | 1 | 2 | 3 | 4 |
| 4. Going up the stairs (one flight) | 0 | 1 | 2 | 3 | 4 |
| 5. Going down the stairs (one flight) | 0 | 1 | 2 | 3 | 4 |
| 6. Standing in prayers (or for short time, less than 5 min) | 0 | 1 | 2 | 3 | 4 |
| 7. Bending to the floor (Bowing) | 0 | 1 | 2 | 3 | 4 |
| 8. Prostrating in prayers | 0 | 1 | 2 | 3 | 4 |
| 9. Kneeling in prayers | 0 | 1 | 2 | 3 | 4 |
| 10. Squatting | 0 | 1 | 2 | 3 | 4 |
| 11. Getting into or out of the car | 0 | 1 | 2 | 3 | 4 |
| 12. Lifting or carrying heavy objects | 0 | 1 | 2 | 3 | 4 |

**D. Social function**

Please indicate how much does your knee problem affects the following social activities

| | | | | | |
|---|---|---|---|---|---|
| 1. Visiting (friends or relatives) | 0 | 1 | 2 | 3 | 4 |
| 2. Attending social events (weddings, etc.) | 0 | 1 | 2 | 3 | 4 |
| 3. Having guests | 0 | 1 | 2 | 3 | 4 |

**E. Emotional function**

Please indicate how much you have been bothered by the following feelings because of your knee problem

| | | | | | |
|---|---|---|---|---|---|
| 1. Feeling low, lacking enthusiasm | 0 | 1 | 2 | 3 | 4 |
| 2. Nervous, anxious | 0 | 1 | 2 | 3 | 4 |
| 3. Easily annoyed, irritated | 0 | 1 | 2 | 3 | 4 |

**APPENDIX VIII(B)ARABIC VERSION)**

# المقياس الوظيفي للركبة

## (SKFS)

مقياس لتحديد مقدار التأثر الوظيفي لدى الأفراد المصابين بالفصال العظمي لمفصل الركبة

**تعليمات**

(يجب قراءتها قبل البدء بالإجابة على الاستبيان)

الاستبيان التالي الذي انت بصدد الإجابة عليه هو عبارة عن مجموعة من الأسئلة التي تفيدنا في تقييم وضع ركبتك. يتكون الاستبيان من خمسة أقسام، القسم الأول يتضمن أسئلة عن شدة الألم الذي تحسه عند قيامك ببعض الأنشطة اليومية. القسم الثاني يتضمن أسئلة عن التيبس الذي يمكن أن تحسه في الركبة. أما القسم الثالث فيضم مجموعة من الأسئلة عن مدى الصعوبة التي تجدها عند قيامك ببعض الأنشطة اليومية بسبب ما تعانيه من تعب في الركبة. القسمان الرابع والخامس يتضمنان أسئلة عن مدى تأثير هذا التعب على نشاطك الاجتماعي وحالتك النفسية. أما عن كيفية الاجابة على الأسئلة، فستجد أمام كل سؤال خمسة خيارات من "0" إلى"4"، ضع دائرة حول الاختيار الذي يناسبك وفي الأسفل مثال للتوضيح وصور لوجوه تعبر عن معنى كل خيار:

**مثال:**

لو كانت الاجابة عن السؤال الأول في القسم الأول، حيث السؤال عن شدة الألم الذي تعاني منه أثناء النوم أو الراحة، كما يلي:

1. في الليل وأنت في الفراش أو أثناء الراحة خلال النهار

لايوجد ألم ألم بسيط ألم معتدل ألم شديد ألم لايحتمل

4 3 2 1 (0)

فإن هذه الإجابة تدل على أن الشخص لا يعاني من ألم في الركبة أثناء الراحة أو النوم. أما إذا كان يعاني من ألم شديد جدا ولا يحتمل فان الإجابة ستكون كما يلي:

1. في الليل وأنت في الفراش أو أثناء الراحة خلال النهار

لايوجد ألم ألم بسيط ألم معتدل ألم شديد ألم لايحتمل

(4) 3 2 1 0

لاحظ أنه كلما اتجهت إلى اليسار كان الألم أشد، هذا ينطبق على الأسئلة الأخرى في جميع الأقسام.

الرجاء الاجابة بدقة على جميع الاسئلة وذلك بوضع دائرة حول الرقم المناسب

**القسم الأول – الألم**

ما هو مقدار الألم الذي تعاني منه بسبب الركبة عند القيام بالأنشطة التالية خلال الثلاثة ايام الماضية:

| | لايوجد ألم | ألم بسيط | ألم معتدل | ألم شديد | ألم لايحتمل |
|---|---|---|---|---|---|
| 1. في الليل وأنت في الفراش أو اثناء الراحة خلال النهار | 0 | 1 | 2 | 3 | 4 |
| 2. عند الجلوس على الأرض أو القيام منها | 0 | 1 | 2 | 3 | 4 |
| 3. عند الجلوس على الكرسي (العادي) أو القيام منه | 0 | 1 | 2 | 3 | 4 |
| 4. عند المشي على أرض منبسطة (لمسافة قصيرة، 50 متر تقريبا) | 0 | 1 | 2 | 3 | 4 |
| 5. عند صعود أو نزول الدرج (أقل من 8 درجات) | 0 | 1 | 2 | 3 | 4 |
| 6. عند الوقوف أثناء الصلاة (أولوقت قصير، أقل من 5 دقائق) | 0 | 1 | 2 | 3 | 4 |
| 7. عند الركوع، السجود، أو الجلوس في الصلاة | 0 | 1 | 2 | 3 | 4 |
| 8. عند جلوس القرفصاء (كالجلوس على المرحاض العربي) | 0 | 1 | 2 | 3 | 4 |

**القسم الثاني – التيبس**

الاسئلة التالية هي لتحديد مقدار التيبس (التصلب وصعوبة الحركة وليس الألم) في الركبة خلال الأيام الثلاثة الماضية:

| | لايوجد | بسيط | معتدل | شديد | لايحتمل |
|---|---|---|---|---|---|
| 1. ما مدى شدة التيبس الذي تحسه في الصباح بعد الاستيقاظ من النوم | 0 | 1 | 2 | 3 | 4 |
| 2. ما مدى شدة التيبس بعد الجلوس الطويل سواء على الأرض أو على الكرسي | 0 | 1 | 2 | 3 | 4 |

**القسم الثالث – الأنشطة الوظيفية (القدرة على الحركة والاعتناء بالنفس)**

مامقدار الصعوبة التي تواجهها بسبب الركبة عند القيام بالأنشطة التالية خلال الأيام الثلاثة الماضية:

| | لايوجد | بسيط | معتدل | شديد | لايحتمل |
|---|---|---|---|---|---|
| 1. المشي على أرض منبسطة | 0 | 1 | 2 | 3 | 4 |
| 2. الجلوس على الأرض أو القيام منها | 0 | 1 | 2 | 3 | 4 |
| 3. الجلوي على الكرسي أو القيام منه | 0 | 1 | 2 | 3 | 4 |
| 4. صعود الدرج | 0 | 1 | 2 | 3 | 4 |
| 5. نزول الدرج | 0 | 1 | 2 | 3 | 4 |
| 6. الوقوف (أثناء الصلاة) | 0 | 1 | 2 | 3 | 4 |
| 7. السجود في الصلاة | 0 | 1 | 2 | 3 | 4 |
| 8. الجلوس في الصلاة | 0 | 1 | 2 | 3 | 4 |
| 9. استخدام المرحاض العربي | 0 | 1 | 2 | 3 | 4 |
| 10. رفع أوحمل الأشياء الثقيلة | 0 | 1 | 2 | 3 | 4 |
| 11. الانحناء على الأرض من وضع الوقوف | 0 | 1 | 2 | 3 | 4 |
| 12. الركوب أو النزول من السيارة | 0 | 1 | 2 | 3 | 4 |

**القسم الرابع – الأنشطة الاجتماعية**

حدد مدى تأثير مشكلة الركبة لديك على الأنشطة الاجتماعية التالية:

| | لاتؤثر | تؤثر نادرا | أحيانا | معظم الأحيان | لا أستطيع |
|---|---|---|---|---|---|
| 1. القيام بزيارة الأقارب والأصدقاء | 0 | 1 | 2 | 3 | 4 |
| 2. حضور الأعراس والولائم | 0 | 1 | 2 | 3 | 4 |
| 3. استقبال الضيوف في البيت | 0 | 1 | 2 | 3 | 4 |

**القسم الخامس – الحالة النفسية**

حدد مقدار تكرر تعرضك للحالات النفسية التالية بسبب مشكلة الركبة لديك:

| | مطلقا | نادرا | أحيانا | معظم الأحيان | دائما |
|---|---|---|---|---|---|
| 1. الشعور بالكآبة وضيق الصدر | 0 | 1 | 2 | 3 | 4 |
| 2. التوتر والقلق | 0 | 1 | 2 | 3 | 4 |
| 3. العصبية وسرعة الغضب | 0 | 1 | 2 | 3 | 4 |

# APPENDIX IX: Demographical information

Today's Date _____/_____/_____ Patient No: .....

Physician's name: .....

Patient's Name:....., Initial Ms Mr Mrs

Birth Date / / Age () Sex F () M ()

Weight: ..... Height: .....

Marital Status: Single () Married ()

Street Address... ..... City:.....Post Code:.....

Phone Number:..... May We Leave a Message?
Yes () No ()

Occupation: Student () Employer ()..... Retired (),

Previous job.....

Employer Phone Number: ...

Onset disease: .....

Have you or an immediate family member ever been told you have the following:

| | Self | Family |
|---|---|---|
| Osteoarthritis | Y N | Y N |
| Cancer | Y N | Y N |
| History of photosensitivity (Adverse reactions to sunlight) | Y N | Y N |
| Diabetes | Y N | Y N |
| High Blood Pressure | Y N | Y N |

Heart Disease Y N Y N

Are you pregnant? Y () N ()

Are your symptoms? () Better () Worse () Same

Do you currently have problems with the following?

() Driving () Walking () Standing () Bending () Lifting () Up from Chair or the floor

Days per week you exercise: 0 1 2 3 4 5 6 7

How are you sleeping at night? Intermittent because of pain () Normal ()

Are you now under medications? No () Yes ().....

Please list any major surgery and hospitalisations: .....

Have you ever had an X-ray for your knee? Yes () No () Result: .....

Have you ever had an MRI/CT scan for your knee? Yes () No ()
Result: .....

Have you ever been treated by Physical Therapist? Yes () No ()

If Yes, When? .....

What were you treated for? .....

What was the result? .....

# APPENDIX X: Visual analogue scale scores

Table1 VAS scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 9 | 5 | 7 | 6 | 7 |
| 2 | 9.5 | 4.5 | 5 | 4 | 2 |
| 3 | 9.5 | 9.5 | 6 | 6 | 5 |
| 4 | 9 | 3 | 1.5 | 3.5 | 3 |
| 5 | 7 | 5 | 3 | 4 | 6 |
| 6 | 5 | 1.5 | 4 | 1.5 | 5 |
| 7 | 9 | 6 | 5 | 3 | 5 |
| 8 | 5 | 3 | 2.5 | 1.5 | 1 |
| 9 | 6 | 3 | 3.5 | 5 | 3 |
| 10 | 5 | 3 | 2.5 | 3 | 5 |
| 11 | 5.5 | 2 | 2 | 2 | 1 |
| 12 | 6 | 1 | 0.5 | 0.5 | 2 |
| 13 | 8 | 8 | 4.5 | 5 | 4 |
| 14 | 4 | 3 | 1.5 | 5 | 2 |
| 15 | 6.5 | 3 | 2 | 1 | 2 |
| 16 | 8 | 5 | 5 | 3.5 | 3 |
| 17 | 7 | 2.5 | 2 | 1 | 2 |
| 18 | 4.5 | 1.5 | 2 | 2 | 2 |
| 19 | 3 | 1 | 1 | 1 | 1 |
| 20 | 5 | 2.5 | 2 | 4 | 4.5 |
| 21 | 8 | 5 | 5 | 3 | 5 |
| 22 | 3.5 | 3 | 1 | 0.5 | 6 |
| 23 | 5 | 4 | 3 | 3.5 | 3 |
| 24 | 5.5 | 1 | 1.5 | 2 | 0.5 |
| 25 | 7.5 | 6 | 5 | 3.5 | 3 |
| 26 | 5 | 5 | 4 | 2 | 4 |
| Total/260 | 166 | 97 | 82 | 77 | 87 |

Total VAS = 10 Scores, 26 subjects x 10 = 260 scores

Table 2 VAS scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 9 | 9.5 | 9 | 8 | 8.5 |
| 2 | 3.5 | 1.5 | 1 | 2 | 1.5 |
| 3 | 5.5 | 7 | 7 | 3.5 | 4 |
| 4 | 5 | 5.5 | 2 | 4 | 2 |
| 5 | 7 | 4 | 3.5 | 3.5 | 6 |
| 6 | 4.5 | 4 | 4 | 6 | 6 |
| 7 | 6 | 2.5 | 2.5 | ٥ | 6 |
| 8 | 4 | 3.5 | 3 | 3 | 5 |
| 9 | 3.5 | 3 | 3 | 5 | 7 |
| 10 | 6 | 7 | 1.5 | ٤ | 2 |
| 11 | 6 | 3 | 2 | 5 | 4 |
| 12 | 4 | 4 | 1.5 | 3 | 4 |
| 13 | 7 | 3 | 1 | 3 | 4 |
| 14 | 6 | 5 | 5 | 5 | 7 |
| 15 | 6.5 | 7 | 7 | 8 | 6 |
| 16 | 9.5 | 9.5 | 9 | 9 | 8.5 |
| 17 | 8.5 | 3 | 3 | 2 | 4.5 |
| 18 | 3.5 | 2.5 | 3 | 3 | 6 |
| 19 | 6 | 7 | 5 | 5 | 2.5 |
| 20 | 8 | 8 | 5 | 5 | 8 |
| 21 | 5 | 5 | 4 | 2.5 | 3 |
| 22 | 6 | 3 | 3 | 2 | 4 |
| 23 | 6 | 2.5 | 2 | 2 | 9 |
| Total/230 | 136 | 110 | 87 | ٩٨.5 | 118.5 |

Total VAS = 10 Scores, 23subjects x 10 = 230 scores

# APPENDIX XI: Saudi knee functional scale (total)

Table1 SKFS (total) for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 94 | 63 | 6٧ | 6٤ | 72 |
| 2 | 89 | 55 | 29 | 24 | 19 |
| 3 | 60 | 55 | 49 | 58 | 41 |
| 4 | 85 | 40 | 26 | 30 | 22 |
| 5 | 81 | 76 | 43 | 3٧ | 51 |
| 6 | 62 | 37 | 27 | 24 | 43 |
| 7 | 92 | 56 | 50 | 68 | 61 |
| 8 | 60 | 18 | 18 | 7 | 5 |
| 9 | 68 | 35 | 21 | 51 | 19 |
| 10 | 34 | 21 | 14 | 7 | 21 |
| 11 | 44 | 8 | 4 | 10 | 8 |
| 12 | 45 | 14 | 2 | 4 | 14 |
| 13 | 81 | 82 | 52 | 63 | 43 |
| 14 | 63 | 37 | 37 | 55 | 23 |
| 15 | 57 | 31 | 21 | 10 | 21 |
| 16 | 64 | 44 | 26 | 31 | 44 |
| 17 | 66 | 39 | 23 | 31 | 34 |
| 18 | 24 | 13 | 10 | 14 | 27 |
| 19 | 23 | 10 | 7 | 12 | 9 |
| 20 | 55 | 35 | 39 | 35 | 38 |
| 21 | 63 | 47 | 43 | 41 | 59 |
| 22 | 40 | 20 | 12 | 12 | 44 |
| 23 | 42 | 39 | 38 | 35 | 35 |
| 24 | 13 | 14 | 6 | 14 | 2 |
| 25 | 65 | 53 | 51 | 33 | 26 |
| 26 | 58 | 35 | 21 | 17 | 36 |
| Total/2912 | 1528 | 977 | 73٦ | 7٨٧ | 817 |

A total of the 5 SKFS subscales = 112 scores,

26 subjects x 112 = 2912 scores

Table 2 SKFS (total) for each participant in the control group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 85 | 88 | 88 | 80 | 84 |
| 2 | 28 | 15 | 14 | 18 | 19 |
| 3 | 84 | 74 | 76 | 63 | 55 |
| 4 | 65 | 65 | 46 | 40 | 21 |
| 5 | 78 | 46 | 57 | 32 | 53 |
| 6 | 46 | 45 | 34 | 58 | 59 |
| 7 | 49 | 15 | 19 | ٢٣ | 33 |
| 8 | 49 | 47 | 45 | 43 | 40 |
| 9 | 58 | 33 | 36 | 49 | 55 |
| 10 | 66 | 62 | 26 | 39 | 32 |
| 11 | 70 | 43 | 41 | 50 | 51 |
| 12 | 70 | 44 | 31 | 40 | 46 |
| 13 | 74 | 38 | 29 | 35 | 51 |
| 14 | 37 | 39 | 49 | 55 | 53 |
| 15 | 48 | 52 | 43 | 51 | 54 |
| 16 | 58 | 54 | 53 | 47 | 56 |
| 17 | 71 | 39 | 36 | 29 | 42 |
| 18 | 27 | 15 | 1 | 17 | 51 |
| 19 | 64 | 71 | 49 | 32 | 31 |
| 20 | 63 | 51 | 60 | 54 | 65 |
| 21 | 57 | 50 | 59 | 55 | 35 |
| 22 | 51 | 9 | 11 | 5 | 21 |
| 23 | 60 | 40 | 30 | 28 | 57 |
| Total/2576 | 1358 | 1035 | 933 | ٩٤٣ | 1064 |

A total of the 5 SKFS subscales = 112 scores,
23 subjects x 112 = 2576 scores

# APPENDIX XII: Saudi knee functional scale (subscales)

## Section A - Pain

Table1 Pain scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 27 | 20 | 24 | 22 | 18 |
| 2 | 28 | 16 | 8 | 7 | 7 |
| 3 | 17 | 17 | 12 | 16 | 11 |
| 4 | 26 | 13 | 6 | 10 | 8 |
| 5 | 20 | 20 | 14 | 13 | 18 |
| 6 | 19 | 9 | 12 | 9 | 13 |
| 7 | 23 | 14 | 13 | 15 | 15 |
| 8 | 16 | 8 | 8 | 3 | 2 |
| 9 | 19 | 7 | 7 | 16 | 8 |
| 10 | 11 | 6 | 4 | 3 | 10 |
| 11 | 14 | 3 | 1 | 5 | 3 |
| 12 | 15 | 5 | 0 | 1 | 6 |
| 13 | 21 | 20 | 12 | 18 | 12 |
| 14 | 16 | 11 | 8 | 15 | 8 |
| 15 | 17 | 11 | 7 | 3 | 5 |
| 16 | 22 | 13 | 9 | 10 | 13 |
| 17 | 18 | 11 | 9 | 8 | 13 |
| 18 | 10 | 6 | 5 | 7 | 10 |
| 19 | 9 | 5 | 4 | 6 | 3 |
| 20 | 15 | 10 | 12 | 10 | 12 |
| 21 | 22 | 19 | 14 | 13 | 18 |
| 22 | 13 | 8 | 5 | 3 | 14 |
| 23 | 13 | 13 | 12 | 11 | 10 |
| 24 | 2 | 4 | 4 | 5 | 0 |
| 25 | 19 | 13 | 13 | 8 | 8 |
| 26 | 15 | 8 | 4 | 4 | 11 |
| Total/832 | 447 | 290 | 227 | 241 | 256 |

Pain subscale contains 8 questions of pain, total scores= 32 scores,

26 subjects x 32 = 832 scores

Table 2 Pain scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 22 | 24 | 22 | 21 | 21 |
| 2 | 9 | 5 | 4 | 5 | 9 |
| 3 | 24 | 20 | 19 | 16 | 15 |
| 4 | 15 | 17 | 12 | 13 | 5 |
| 5 | 22 | 11 | 13 | 9 | 16 |
| 6 | 15 | 16 | 12 | 19 | 18 |
| 7 | 15 | 5 | 7 | 10 | 15 |
| 8 | 14 | 12 | 13 | 13 | 15 |
| 9 | 17 | 7 | 9 | 13 | 16 |
| 10 | 21 | 19 | 9 | 12 | 12 |
| 11 | 20 | 10 | 9 | 11 | 12 |
| 12 | 17 | 9 | 9 | 14 | 14 |
| 13 | 21 | 12 | 10 | 9 | 19 |
| 14 | 11 | 10 | 16 | 20 | 18 |
| 15 | 12 | 14 | 11 | 14 | 13 |
| 16 | 16 | 15 | 14 | 17 | 18 |
| 17 | 21 | 11 | 9 | 8 | 11 |
| 18 | 8 | 5 | 1 | 6 | 15 |
| 19 | 20 | 24 | 16 | 11 | 13 |
| 20 | 19 | 15 | 16 | 17 | 19 |
| 21 | 15 | 11 | 9 | 13 | 10 |
| 22 | 15 | 5 | 2 | 2 | 9 |
| 23 | 17 | 11 | 10 | 12 | 17 |
| Total/736 | 386 | 288 | 252 | 285 | 330 |

Pain subscale contains 8 questions of pain, total scores= 32 scores,

23 subjects x 32 = 736 scores

## Section B - Stiffness

Table 3 Stiffness scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 8 | 4 | ٢ | ٣ | 5 |
| 2 | 8 | 2 | 0 | 1 | 1 |
| 3 | 6 | 6 | 4 | 4 | 3 |
| 4 | 6 | 2 | 0 | 2 | 1 |
| 5 | 6 | 6 | 6 | ٤ | 4 |
| 6 | 2 | 3 | 3 | 2 | 4 |
| 7 | 6 | 4 | 2 | 6 | 4 |
| 8 | 6 | 2 | 0 | 0 | 0 |
| 9 | 4 | 6 | 3 | 3 | 0 |
| 10 | 4 | 4 | 1 | 0 | 2 |
| 11 | 6 | 0 | 0 | 2 | 1 |
| 12 | 5 | 2 | 1 | 1 | 1 |
| 13 | 8 | 6 | 4 | 5 | 4 |
| 14 | 4 | 2 | 2 | 4 | 2 |
| 15 | 6 | 4 | 2 | 0 | 0 |
| 16 | 5 | 5 | 2 | 4 | 5 |
| 17 | 6 | 2 | 2 | 4 | 3 |
| 18 | 0 | 0 | 0 | 0 | 1 |
| 19 | 4 | 2 | 0 | 1 | 1 |
| 20 | 4 | 6 | 2 | 2 | 2 |
| 21 | 6 | 0 | 0 | 2 | 5 |
| 22 | 4 | 4 | 1 | 2 | 4 |
| 23 | 4 | 3 | 4 | 4 | 3 |
| 24 | 4 | 0 | 0 | 1 | 0 |
| 25 | 5 | 6 | 6 | 2 | 2 |
| 26 | 4 | 2 | 2 | 2 | 3 |
| Total/208 | 131 | 83 | ٤٩ | ٦١ | 61 |

Stiffness subscale contains 2 questions of stiffness, total scores= 8 scores,

26 subjects x 8 = 208 scores

Table 4 Stiffness scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 7 | 8 | 8 | 8 | 8 |
| 2 | 1 | 0 | 0 | 2 | 0 |
| 3 | 6 | 4 | 6 | 4 | 3 |
| 4 | 6 | 4 | 4 | 6 | 3 |
| 5 | 6 | 1 | 4 | 0 | 2 |
| 6 | 4 | 3 | 2 | 5 | 4 |
| 7 | 5 | 2 | 2 | ٥ | 2 |
| 8 | 4 | 1 | 1 | 2 | 1 |
| 9 | 4 | 4 | 3 | 6 | 4 |
| 10 | 6 | 6 | 2 | 4 | 1 |
| 11 | 5 | 1 | 1 | 1 | 1 |
| 12 | 4 | 2 | 0 | 2 | 2 |
| 13 | 6 | 0 | 2 | 3 | 2 |
| 14 | 6 | 5 | 6 | 6 | 6 |
| 15 | 5 | 6 | 4 | 6 | 3 |
| 16 | 4 | 6 | 6 | 4 | 5 |
| 17 | 6 | 6 | 4 | 4 | 2 |
| 18 | 2 | 0 | 0 | 2 | 4 |
| 19 | 6 | 6 | 4 | 2 | 1 |
| 20 | 5 | 4 | 6 | 4 | 5 |
| 21 | 6 | 3 | 6 | 4 | 2 |
| 22 | 6 | 1 | 1 | 0 | 0 |
| 23 | 6 | 5 | 2 | 1 | 6 |
| Total/184 | 116 | 78 | 74 | ٨١ | 67 |

Stiffness subscale contains 2 questions of stiffness, total scores= 8 scores,
23 subjects x 8 = 184 scores

## Section C - Physical Function

Table 5 Physical Function scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 44 | 30 | 30 | 29 | 31 |
| 2 | 36 | 24 | 14 | 15 | 7 |
| 3 | 35 | 32 | 29 | 27 | 18 |
| 4 | 39 | 14 | 12 | 15 | 13 |
| 5 | 35 | 33 | 17 | 14 | 18 |
| 6 | 27 | 16 | 12 | 13 | 16 |
| 7 | 40 | 25 | 19 | 29 | 26 |
| 8 | 27 | 7 | 10 | 4 | 3 |
| 9 | 27 | 12 | 7 | 23 | 8 |
| 10 | 15 | 11 | 9 | 4 | 9 |
| 11 | 22 | 5 | 3 | 3 | 4 |
| 12 | 19 | 7 | 1 | 2 | 6 |
| 13 | 33 | 34 | 22 | 23 | 15 |
| 14 | 26 | 17 | 15 | 25 | 10 |
| 15 | 28 | 16 | 12 | 7 | 10 |
| 16 | 25 | 17 | 12 | 13 | 21 |
| 17 | 30 | 17 | 10 | 14 | 14 |
| 18 | 14 | 4 | 5 | 7 | 11 |
| 19 | 6 | 3 | 3 | 4 | 3 |
| 20 | 25 | 13 | 19 | 17 | 16 |
| 21 | 29 | 28 | 26 | 26 | 32 |
| 22 | 20 | 8 | 6 | 7 | 21 |
| 23 | 19 | 18 | 17 | 14 | 14 |
| 24 | 7 | 10 | 2 | 8 | 2 |
| 25 | 29 | 22 | 23 | 15 | 11 |
| 26 | 22 | 9 | 9 | 6 | 14 |
| Total/1248 | 679 | 432 | 344 | 364 | 353 |

Physical Function subscale contains 12 questions of physical activities, total scores = 48 scores, 26 subjects x 48 = 1248 scores

Table 6 Physical Function scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 33 | 33 | 35 | 33 | 37 |
| 2 | 16 | 10 | 10 | 11 | 10 |
| 3 | 37 | 35 | 34 | 26 | 25 |
| 4 | 29 | 29 | 19 | 18 | 13 |
| 5 | 37 | 21 | 27 | 14 | 23 |
| 6 | 23 | 26 | 18 | 28 | 30 |
| 7 | 19 | 8 | 9 | 8 | 16 |
| 8 | 21 | 23 | 20 | 19 | 20 |
| 9 | 27 | 18 | 18 | 19 | 24 |
| 10 | 27 | 24 | 11 | 15 | 17 |
| 11 | 30 | 18 | 19 | 23 | 27 |
| 12 | 32 | 23 | 19 | 21 | 23 |
| 13 | 30 | 18 | 17 | 19 | 24 |
| 14 | 14 | 15 | 19 | 24 | 17 |
| 15 | 21 | 22 | 17 | 26 | 27 |
| 16 | 27 | 27 | 21 | 22 | 27 |
| 17 | 30 | 19 | 20 | 16 | 18 |
| 18 | 14 | 4 | 0 | 9 | 23 |
| 19 | 29 | 32 | 26 | 17 | 15 |
| 20 | 24 | 18 | 25 | 20 | 28 |
| 21 | 20 | 22 | 23 | 23 | 16 |
| 22 | 24 | 3 | 8 | 3 | 10 |
| 23 | 26 | 16 | 14 | 14 | 24 |
| Total/1104 | 590 | 464 | 429 | 428 | 494 |

Physical Function subscale contains 12 questions of physical activities, total scores = 48 scores, 23 subjects x 48 = 1104 scores

## Section D - Social Function

Table 7 Social Function scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 10 | 8 | 7 | 6 | 9 |
| 2 | 8 | 7 | 7 | 1 | 4 |
| 3 | 1 | 0 | 2 | 6 | 6 |
| 4 | 8 | 6 | 5 | 3 | 0 |
| 5 | 11 | 8 | 0 | 0 | 5 |
| 6 | 6 | 6 | 0 | 0 | 6 |
| 7 | 11 | 7 | 8 | 9 | 7 |
| 8 | 7 | 0 | 0 | 0 | 0 |
| 9 | 9 | 5 | 3 | 0 | 1 |
| 10 | 0 | 0 | 0 | 0 | 0 |
| 11 | 0 | 0 | 0 | 0 | 0 |
| 12 | 0 | 0 | 0 | 0 | 0 |
| 13 | 10 | 11 | 8 | 9 | 6 |
| 14 | 8 | 3 | 6 | 7 | 3 |
| 15 | 6 | 0 | 0 | 0 | 3 |
| 16 | 3 | 3 | 3 | 2 | 3 |
| 17 | 3 | 3 | 0 | 0 | 1 |
| 18 | 0 | 3 | 0 | 0 | 3 |
| 19 | 0 | 0 | 0 | 0 | 1 |
| 20 | 7 | 6 | 6 | 6 | 4 |
| 21 | 6 | 0 | 3 | 0 | 4 |
| 22 | 0 | 0 | 0 | 0 | 2 |
| 23 | 0 | 0 | 0 | 0 | 3 |
| 24 | 0 | 0 | 0 | 0 | 0 |
| 25 | 6 | 6 | 6 | 6 | 3 |
| 26 | 8 | 7 | 3 | 3 | 4 |
| Total/312 | 128 | 89 | 67 | 58 | 78 |

Social Function subscale contains 3 questions of social activities, total scores = 12 scores,

26 subjects x 12 = 312 scores

Table 8 Social Function scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 11 | 11 | 11 | 9 | 9 |
| 2 | 0 | 0 | 0 | 0 | 0 |
| 3 | 9 | 8 | 8 | 8 | 6 |
| 4 | 11 | 9 | 4 | 3 | 0 |
| 5 | 8 | 8 | 6 | 3 | 6 |
| 6 | 4 | 0 | 2 | 6 | 3 |
| 7 | 6 | 0 | 0 | 0 | 0 |
| 8 | 6 | 7 | 6 | 5 | 1 |
| 9 | 6 | 3 | 6 | 9 | 6 |
| 10 | 5 | 8 | 3 | 7 | 0 |
| 11 | 6 | 8 | 8 | 9 | 5 |
| 12 | 8 | 6 | 1 | 3 | 5 |
| 13 | 8 | 3 | 0 | 4 | 6 |
| 14 | 0 | 3 | 3 | 2 | 6 |
| 15 | 6 | 5 | 6 | 5 | 5 |
| 16 | 6 | 6 | 6 | 3 | 6 |
| 17 | 8 | 3 | 3 | 0 | 6 |
| 18 | 0 | 0 | 0 | 0 | 6 |
| 19 | 3 | 3 | 3 | 1 | 0 |
| 20 | 6 | 6 | 6 | 6 | 6 |
| 21 | 7 | 8 | 12 | 6 | 3 |
| 22 | 0 | 0 | 0 | 0 | 0 |
| 23 | 6 | 3 | 3 | 0 | 5 |
| Total/276 | 130 | 108 | 97 | 89 | 90 |

Social Function subscale contains three questions of social activities, total scores = 12 scores, 23 subjects x 12 = 276 scores

## Section E- Emotional function

Table 9 Emotional function scores for each participant in the active group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 5 | 1 | 4 | 4 | 9 |
| 2 | 9 | 6 | 0 | 0 | 0 |
| 3 | 1 | 0 | 2 | 5 | 3 |
| 4 | 6 | 5 | 3 | 0 | 0 |
| 5 | 9 | 9 | 6 | 6 | 6 |
| 6 | 8 | 3 | 0 | 0 | 4 |
| 7 | 12 | 6 | 8 | 9 | 9 |
| 8 | 4 | 1 | 0 | 0 | 0 |
| 9 | 9 | 5 | 1 | 9 | 2 |
| 10 | 4 | 0 | 0 | 0 | 0 |
| 11 | 2 | 0 | 0 | 0 | 0 |
| 12 | 6 | 0 | 0 | 0 | 1 |
| 13 | 9 | 11 | 6 | 8 | 6 |
| 14 | 9 | 4 | 6 | 4 | 0 |
| 15 | 0 | 0 | 0 | 0 | 3 |
| 16 | 9 | 6 | 0 | 2 | 2 |
| 17 | 9 | 6 | 2 | 5 | 3 |
| 18 | 0 | 0 | 0 | 0 | 2 |
| 19 | 4 | 0 | 0 | 1 | 1 |
| 20 | 4 | 0 | 0 | 0 | 4 |
| 21 | 0 | 0 | 0 | 0 | 0 |
| 22 | 3 | 0 | 0 | 0 | 3 |
| 23 | 6 | 5 | 5 | 6 | 5 |
| 24 | 0 | 0 | 0 | 0 | 0 |
| 25 | 6 | 6 | 3 | 2 | 2 |
| 26 | 9 | 9 | 3 | 2 | 4 |
| Total/312 | 143 | 83 | 49 | 63 | 69 |

Emotional function subscale contains three questions about the Psychological status, total scores = 12 scores, 26 subjects x 12 =312 scores

Table 10 Emotional function scores for each participant in the control group for all study periods

| Subject ID | Baseline | 5 Sessions | 9 Sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 12 | 12 | 12 | 9 | 9 |
| 2 | 2 | 0 | 0 | 0 | 0 |
| 3 | 8 | 7 | 9 | 9 | 6 |
| 4 | 4 | 6 | 7 | 0 | 0 |
| 5 | 5 | 5 | 7 | 6 | 6 |
| 6 | 0 | 0 | 0 | 0 | 4 |
| 7 | 4 | 0 | 1 | 0 | 0 |
| 8 | 4 | 4 | 5 | 4 | 3 |
| 9 | 4 | 1 | 0 | 2 | 5 |
| 10 | 7 | 5 | 1 | 1 | 2 |
| 11 | 9 | 6 | 4 | 6 | 6 |
| 12 | 9 | 4 | 2 | 0 | 2 |
| 13 | 9 | 5 | 0 | 0 | 0 |
| 14 | 6 | 6 | 5 | 3 | 6 |
| 15 | 4 | 5 | 5 | 0 | 6 |
| 16 | 5 | 0 | 6 | 1 | 0 |
| 17 | 6 | 0 | 0 | 1 | 5 |
| 18 | 3 | 6 | 0 | 0 | 3 |
| 19 | 6 | 6 | 0 | 1 | 2 |
| 20 | 9 | 8 | 7 | 7 | 7 |
| 21 | 9 | 6 | 9 | 9 | 4 |
| 22 | 6 | 0 | 0 | 0 | 2 |
| 23 | 5 | 5 | 1 | 1 | 5 |
| Total/276 | 136 | 97 | 81 | 60 | 83 |

Emotional function subscale contains three questions about the Psychological status, total scores = 12 scores, 23 subjects x 12 =276 scores

# APPENDIX XIII: Raw data

Table1 Raw data for the active group

| ID | Sex | Age | Height | Wight | BMI | Affected knee | Level of Education | Occupation | Start Symptoms |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 60 | 164 | 90 | 39 | Lt | Educated | Retired | 4 |
| 2 | F | 56 | 152 | 88.7 | 38.3 | Lt | Uneducated | Housewife | 5 |
| 3 | M | 65 | 153.5 | 67 | 30 | Lt | Uneducated | Retired | 3 |
| 4 | F | 55 | 148 | 66.6 | 30.4 | Rt | Uneducated | Housewife | 5 |
| 5 | F | 48 | 158 | 87.6 | 35 | Lt | Uneducated | Housewife | 5 |
| 6 | F | 51 | 151 | 91.6 | 40.1 | Rt | Educated | Retired | 2 |
| 7 | M | 56 | 163.5 | 90.2 | 40 | Lt | Uneducated | Work | 5 |
| 8 | F | 37 | 161 | 103.3 | 45.9 | Lt | Educated | Housewife | 1 |
| 9 | F | 46 | 148 | 65.6 | 29 | Rt | Educated | Work | 1 |
| 10 | M | 55 | 156 | 64.5 | 28.3 | Lt | Educated | Retired | 2 |
| 11 | M | 43 | 179.5 | 113.7 | 50.5 | Lt | Uneducated | Work | 2 |
| 12 | M | 38 | 158.5 | 89 | 39.5 | Lt | Educated | Work | 4 |
| 13 | F | 42 | 148.8 | 81.5 | 38.8 | Rt | Educated | Housewife | 4 |
| 14 | F | 71 | 157.2 | 87.4 | 35.3 | Lt | Uneducated | Housewife | 3 |
| 15 | F | 65 | 157.5 | 87.7 | 35.3 | Lt | Uneducated | Housewife | 4 |
| 16 | F | 49 | 158.2 | 87.8 | 35.1 | Rt | Uneducated | Housewife | 6 |
| 17 | M | 61 | 162.5 | 90.2 | 40 | Lt | Uneducated | Retired | 3 |
| 18 | F | 43 | 155.2 | 79.5 | 35.3 | Lt | Uneducated | Housewife | 4 |
| 19 | M | 49 | 163 | 89.5 | 38 | Lt | Educated | Work | 4 |
| 20 | F | 69 | 157 | 87.2 | 35.1 | Rt | Uneducated | Housewife | 4 |
| 21 | F | 52 | 151.3 | 102.9 | 45.7 | Lt | Uneducated | Work | 3 |
| 22 | M | 51 | 167.5 | 89.1 | 39.6 | Rt | Educated | Work | 2 |
| 23 | F | 55 | 168 | 105.1 | 46.7 | Lt | Uneducated | Work | 2 |
| 24 | F | 54 | 152 | 76.5 | 34 | Rt | Educated | Work | 3 |
| 25 | F | 51 | 149.5 | 84.4 | 37.5 | Rt | Uneducated | Housewife | 5 |
| 26 | M | 38 | 160.5 | 101.7 | 45.2 | Rt | Educated | Work | 3 |

Table 2 Raw data for the control group

| ID | Sex | Age | Height | Wight | BMI | Affected knee | Level of Education | Occupation | Start Symptoms |
|---|---|---|---|---|---|---|---|---|---|
| 1 | F | 46 | 148.5 | 81.1 | 38.5 | Rt | Uneducated | Housewife | 2 |
| 2 | M | 44 | 160 | 89 | 39.3 | Rt | Educated | Work | 3 |
| 3 | F | 70 | 157 | 87.2 | 35.1 | Lt | Uneducated | Housewife | 3 |
| 4 | F | 63 | 157.5 | 87.7 | 35.3 | Lt | Educated | Retired | 3 |
| 5 | F | 65 | 156 | 73.1 | 32.4 | Lt | Uneducated | Housewife | 6 |
| 6 | M | 65 | 157 | 64.5 | 28.6 | Lt | Educated | Retired | 2 |
| 7 | F | 42 | 165.2 | 80.5 | 34.3 | Lt | Uneducated | Housewife | 4 |
| 8 | M | 62 | 150.3 | 78.5 | 34.7 | Lt | Educated | Retired | 2 |
| 9 | M | 65 | 158.5 | 77.6 | 34.4 | Lt | Educated | Retired | 2 |
| 10 | F | 37 | 160.1 | 93.9 | 41.7 | Lt | Uneducated | Housewife | 3 |
| 11 | F | 54 | 145.3 | 89.3 | 39.6 | Lt | Educated | Work | 2 |
| 12 | F | 57 | 149.1 | 84.3 | 37.3 | Lt | Uneducated | Housewife | 2 |
| 13 | F | 62 | 150.6 | 88.2 | 39.2 | Rt | Uneducated | Housewife | 3 |
| 14 | F | 48 | 158 | 87.6 | 35 | Lt | Uneducated | Housewife | 5 |
| 15 | M | 68 | 171 | 109.5 | 48.6 | Rt | Educated | Retired | 4 |
| 16 | M | 66 | 153 | 66.5 | 29.5 | Lt | Uneducated | Retired | 4 |
| 17 | M | 67 | 164 | 107.7 | 47.8 | Lt | Uneducated | Retired | 4 |
| 18 | M | 67 | 157 | 64.5 | 28.6 | Lt | Educated | Retired | 3 |
| 19 | F | 62 | 148 | 98.6 | 43.8 | Rt | Uneducated | Housewife | 3 |
| 20 | F | 58 | 149.5 | 84.6 | 37.6 | Rt | Uneducated | Housewife | 1 |
| 21 | F | 45 | 154.5 | 79.5 | 35.3 | Lt | Uneducated | Housewife | 2 |
| 22 | F | 34 | 157.8 | 76.1 | 33.8 | Rt | Uneducated | Housewife | 2 |
| 23 | F | 44 | 147.5 | 95 | 42.2 | Rt | Uneducated | Housewife | 2 |

# APPENDIX XIV: Range of motion

Table1 ROM for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 135 | 138 | 140 | 140 | 136 |
| 2 | 138 | 142 | 145 | 140 | 145 |
| 3 | 138 | 143 | 144 | 138 | 140 |
| 4 | 130 | 142 | 145 | 140 | 137 |
| 5 | 128 | 140 | 140 | 135 | 135 |
| 6 | 133 | 135 | 135 | 133 | 135 |
| 7 | 122 | 132 | 133 | 130 | 130 |
| 8 | 130 | 139 | 136 | 136 | 140 |
| 9 | 130 | 140 | 138 | 130 | 138 |
| 10 | 145 | 145 | 145 | 145 | 145 |
| 11 | 138 | 140 | 145 | 145 | 145 |
| 12 | 130 | 138 | 140 | 140 | 140 |
| 13 | 128 | 129 | 131 | 134 | 140 |
| 14 | 123 | 135 | 130 | 120 | 135 |
| 15 | 125 | 133 | 135 | 135 | 132 |
| 16 | 126 | 130 | 132 | 140 | 140 |
| 17 | 138 | 145 | 145 | 145 | 140 |
| 18 | 130 | 138 | 138 | 138 | 135 |
| 19 | 145 | 145 | 145 | 145 | 145 |
| 20 | 120 | 130 | 125 | 128 | 130 |
| 21 | 120 | 133 | 125 | 122 | 115 |
| 22 | 132 | 135 | 140 | 140 | 135 |
| 23 | 112 | 105 | 110 | 100 | 115 |
| 24 | 130 | 135 | 140 | 138 | 136 |
| 25 | 95 | 100 | 110 | 110 | 115 |
| 26 | 130 | 135 | 138 | 135 | 135 |
| Total | 3351 | 3502 | 3530 | 3482 | 3514 |

Table 2 ROM for each participant in the control group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 132 | 132 | 135 | 128 | 130 |
| 2 | 143 | 144 | 143 | 143 | 143 |
| 3 | 122 | 128 | 125 | 125 | 129 |
| 4 | 135 | 138 | 137 | 125 | 130 |
| 5 | 128 | 130 | 133 | 140 | 135 |
| 6 | 130 | 129 | 130 | 130 | 125 |
| 7 | 132 | 139 | 138 | 135 | 130 |
| 8 | 130 | 135 | 138 | 135 | 130 |
| 9 | 135 | 138 | 140 | 135 | 130 |
| 10 | 128 | 95 | 103 | 110 | 110 |
| 11 | 125 | 133 | 132 | 125 | 130 |
| 12 | 133 | 140 | 142 | 140 | 140 |
| 13 | 132 | 140 | 138 | 143 | 140 |
| 14 | 128 | 130 | 132 | 130 | 127 |
| 15 | 128 | 132 | 132 | 138 | 138 |
| 16 | 138 | 142 | 142 | 140 | 140 |
| 17 | 122 | 122 | 122 | 125 | 125 |
| 18 | 145 | 145 | 145 | 145 | 138 |
| 19 | 115 | 110 | 106 | 115 | 110 |
| 20 | 135 | 130 | 135 | 130 | 127 |
| 21 | 130 | 135 | 130 | 135 | 135 |
| 22 | 130 | 132 | 135 | 140 | 138 |
| 23 | 95 | 130 | 130 | 130 | 93 |
| Total | 2971 | 3029 | 3043 | 3042 | 2973 |

# APPENDIX XV: Knee circumference

Table1 KC for each participant in the active group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 41.5 | 40 | 39.5 | 40 | 39 |
| 2 | 40 | 40 | 40 | 40.5 | 41 |
| 3 | 38 | 38 | 38 | 38 | 38 |
| 4 | 40 | 40 | 38.5 | 40.5 | 40 |
| 5 | 48 | 48 | 46 | 48 | 47.5 |
| 6 | 46.5 | 48 | 49 | 48.5 | 49.5 |
| 7 | 39.5 | 39 | 39.5 | 38.5 | 38 |
| 8 | 46.5 | 46 | 46.5 | 46 | 46.5 |
| 9 | 41 | 40 | 39.5 | 39.5 | 39 |
| 10 | 34.5 | 34 | 35 | 35 | 35 |
| 11 | 43.5 | 43.5 | 44 | 44 | 44 |
| 12 | 42 | 42 | 41.5 | 42 | 43 |
| 13 | 49.5 | 49.5 | 50 | 49.5 | 49.5 |
| 14 | 46.5 | 46.5 | 47.5 | 47.5 | 47 |
| 15 | 50 | 49.5 | 46 | 47 | 47.5 |
| 16 | 47.5 | 48 | 48 | 48.5 | 49 |
| 17 | 42.3 | 42.5 | 42 | 42.5 | 42 |
| 18 | 40 | 39 | 39.5 | 39.5 | 39 |
| 19 | 38 | 38 | 38 | 38 | 38 |
| 20 | 45.5 | 45.5 | 45 | 46.5 | 47 |
| 21 | 50 | 48 | 49.5 | 48.5 | 48.5 |
| 22 | 40.5 | 40 | 40 | 40 | 40 |
| 23 | 44.5 | 44.5 | 44.5 | 44 | 45 |
| 24 | 41 | 41.5 | 42 | 42 | 40 |
| 25 | 45.5 | 45 | 45 | 45.5 | 45 |
| 26 | 45 | 45 | 45.5 | 45.5 | 45.5 |
| Total | 1126.8 | 1121 | 1119.5 | 1125 | 1123.5 |

Table 2 KC for each participant in the control group for all study periods

| Subject ID | Baseline | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|---|
| 1 | 50 | 50 | 50 | 50 | 51.5 |
| 2 | 41.5 | 41.5 | 41.5 | 41.5 | 38 |
| 3 | 49 | 47.5 | 47.5 | 47 | 46 |
| 4 | 48 | 48.5 | 48.5 | 50 | 49 |
| 5 | 39.5 | 39.5 | 39.5 | 39.5 | 39 |
| 6 | 37 | 38 | 37.5 | 38 | 36.5 |
| 7 | 40 | 39.5 | 40 | 40 | 39.3 |
| 8 | 40.5 | 39.5 | 40 | 39 | 39.3 |
| 9 | 39.5 | 39.5 | 39.5 | 39 | 39 |
| 10 | 51 | 49.5 | 49 | 49.5 | 47.5 |
| 11 | 37 | 37.5 | 37.5 | 37 | 37 |
| 12 | 34.5 | 34.5 | 34 | 35 | 35.5 |
| 13 | 46.5 | 46.5 | 46.5 | 46.5 | 45.3 |
| 14 | 48 | 47.5 | 47.5 | 48 | 47 |
| 15 | 47.5 | 45 | 46 | 45.5 | 45 |
| 16 | 38.5 | 37.5 | 38 | 38 | 38 |
| 17 | 47 | 46.5 | 46 | 47 | 47 |
| 18 | 37.5 | 37 | 36.5 | 37 | 36.8 |
| 19 | 43.5 | 45.5 | 43.5 | 43 | 44 |
| 20 | 46.5 | 46.5 | 45 | 45.5 | 45 |
| 21 | 42.5 | 41 | 40.5 | 43 | 43 |
| 22 | 40 | 39 | 39.5 | 39.5 | 40 |
| 23 | 47.5 | 47 | 46 | 48.5 | 49 |
| Total | 992.5 | 984 | 979.5 | 987 | 977.7 |

# APPENDIX XVI: Patient Satisfaction

Table1 Patient Satisfaction for each participant in the active group for all study periods.

| Subject ID | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|
| 1 | 15 | 30 | 35 | 10 |
| 2 | 50 | 70 | 75 | 80 |
| 3 | 0 | 0 | 0 | 30 |
| 4 | 60 | 65 | 70 | 50 |
| 5 | 0 | 65 | 35 | 50 |
| 6 | 50 | 60 | 65 | 30 |
| 7 | 30 | 30 | 45 | 30 |
| 8 | 15 | 55 | 40 | 100 |
| 9 | 50 | 85 | 70 | 80 |
| 10 | 40 | 60 | 70 | 40 |
| 11 | 40 | 25 | 0 | 55 |
| 12 | 70 | 90 | 90 | 90 |
| 13 | 20 | 20 | 20 | 30 |
| 14 | 30 | 45 | 40 | 30 |
| 15 | 80 | 80 | 80 | 50 |
| 16 | 30 | 30 | 30 | 75 |
| 17 | 15 | 20 | 30 | 20 |
| 18 | 50 | 40 | 50 | 50 |
| 19 | 70 | 75 | 70 | 80 |
| 20 | 50 | 60 | 40 | 50 |
| 21 | 30 | 50 | 70 | 30 |
| 22 | 40 | 50 | 80 | 50 |
| 23 | 20 | 20 | 30 | 60 |
| 24 | 40 | 50 | 20 | 90 |
| 25 | 20 | 15 | 70 | 50 |
| 26 | 20 | 20 | 70 | 70 |
| Total | 935 | 1210 | 1295 | 1380 |

Table 2 Patient Satisfaction for each participant in the control group for all study periods

| Subject ID | 5 sessions | 9 sessions | After Six Weeks | After Six Months |
|---|---|---|---|---|
| 1 | 10 | 10 | 0 | 10 |
| 2 | 30 | 55 | 45 | 50 |
| 3 | 0 | 15 | 20 | 30 |
| 4 | 50 | 50 | 50 | 70 |
| 5 | 30 | 35 | 45 | 30 |
| 6 | 0 | 0 | 10 | 0 |
| 7 | 60 | 60 | 40 | 0 |
| 8 | 0 | 20 | 20 | 10 |
| 9 | 0 | 0 | 0 | 10 |
| 10 | 20 | 60 | 45 | 60 |
| 11 | 50 | 85 | 75 | 30 |
| 12 | 10 | 15 | 40 | 10 |
| 13 | 30 | 80 | 50 | 20 |
| 14 | 15 | 50 | 30 | 10 |
| 15 | 0 | 0 | 0 | 40 |
| 16 | 0 | 0 | 0 | 10 |
| 17 | 60 | 80 | 90 | 30 |
| 18 | 60 | 70 | 50 | 10 |
| 19 | 0 | 50 | 50 | 75 |
| 20 | 10 | 10 | 15 | 10 |
| 21 | 25 | 20 | 50 | 30 |
| 22 | 50 | 50 | 70 | 30 |
| 23 | 10 | 40 | 70 | 0 |
| Total | 520 | 855 | 865 | 575 |

# APPENDIX XVII: Comparison between the current study and Hinman *et al.* (2012)

| | **Hinman *et al.* (2012)** | **The current study** |
|---|---|---|
| **Design** | A two-stage Zelen* design RCT (ongoing trial) | DBRCT, (completed) |
| **Purpose** | To investigate the efficacy of needle and laser acupuncture in people with chronic knee pain and to evaluate maintenance of effects over the long-term. Also evaluate the cost-effectiveness of the needle and laser acupuncture and explore whether psychosocial measures are associated with changes in pain, physical function and health-related quality of life following acupuncture treatment. | To evaluate the efficacy of LLLT when it is applied to specific acupuncture points (APs) at the knee joint in combination with exercises and advice in patients with KOA |
| **Quality** | CONSORT; STRICTA guidelines for acupuncture studies | CONSORT, World Association for Laser Therapy (WALT) recommendation |
| **Participants and groups** | 282 men and women<br>**A:** no treatment<br>**B:** Needle acupuncture<br>**C:** Laser acupuncture<br>**D:** placebo laser acupuncture | 49 men and women completed the study<br>**A:** 26 received active laser, exercise and advice<br>**B:** 23 received placebo laser, exercise and advice |
| **Location** | Melbourne and regional Victoria, Australia; multicentre | Security Forces Hospital, Riyadh, Saudi Arabia |
| **Recruitment strategy** | A number of recruitment strategies were used. | One strategy was used |
| **Inclusion and exclusion criteria** | Rigorous | Rigorous |
| **Ethical approval** | Granted | Granted |

| | | |
|---|---|---|
| **Written informed consent** | Provided | Provided |
| **Randomisation** | More than once | Direct |
| **Assessments** | Baseline, 12 weeks and 12 months | Baseline, 5 sessions, last session, 6 weeks, and 6 months |
| **Blinding** | Partial blinding,<br>*The trial laser machine had a small red non-laser light source arising from inside the probe tip that lit up when the probe was in both treatment mode and sham mode (no output). | Full blinding,<br>* same |
| **Primary outcomes** | 1- Pain via an 11-point numeric rating scale (NRS)<br>2- Self-reported physical function via WOMAC. | 1- Pain via VAS |
| **Secondary outcomes** | Quality of life, global rating of change scores and additional measures of pain (other NRS and WOMAC subscale) and physical function (NRS).<br><br>*All outcomes are collected via self-report questionnaire and mailed back to the investigators. | 1- Quality of life via SKFS<br>2-ROM via goniometry<br>3-KC via measure tape<br>4-patient satisfaction (%) |
| **Power calculation** | Yes | Yes |
| **Research operators experience** | Described | Described |
| **Irradiation area** | Mixed of local points (SP9, SP10, ST34, ST35, ST36, LR7, LR8, LR 9, KI10<br>BL39, BL40, BL 57, GB34, GB35, GB36; Distal points, Segmental points, Non-segmental and general points | Five APs (ST 35, Xiyan, ST 36, SP9, and SP10) on the affected knee |
| **Treatment duration** | Acupuncture treatments (approximately 20 minutes in duration) were | A series of 9 treatment sessions was given to each patient over 3 |

| | | |
|---|---|---|
| | administered once or twice weekly (at the GP's discretion) in the GP's rooms for 12 weeks, with a minimum of 8 and a maximum of 12 treatments delivered. | weeks, 3 times a week. In the active laser group, an active continuous laser beam irradiated each point for 40s with a dose of 1.2 J/point. |
| **Laser parameters** | **Output power:** 10 mW<br>**Dose:** 0.2 J per acupuncture point | **Type and wavelength:** GaAlAs, 830nm<br>-Continued wave<br>**Output power:** 30 mW<br>**Dose:** 1.2 J/point X 40 s<br>**Spot area:** 0.28 $cm^2$<br>-Contact technique |
| **Result** | Ongoing | A statistically significant improvement in the laser group compared to the placebo group in the primary outcome VAS and all other outcomes at endpoint assessment except KC. |
| **Conclusion** | The findings of this study will help determine whether laser and/or needle acupuncture are efficacious in relieving knee pain and/or improving physical function. It will also determine whether effects of acupuncture can be maintained over the longer term, and whether psychosocial factors influence treatment outcomes. Importantly, the use of the Zelen design will minimise the bias typically encountered in traditionally designed RCTs where participant expectations may influence study outcomes. | The results demonstrate that the short-period application of LLLT on specific APs associated with exercises and advice is effective in reducing pain and improving the QoL in patients with KOA. |

# APPENDIX XVII: Publications, conferences, and courses

1- Al Rashoud AS, Abboud RJ, Wang W, Wigderowitz C (2014). Efficacy of low-level laser therapy applied at acupuncture points in knee osteoarthritis: a randomised double-blind comparative trial. Physiotherapy, in press, available online 15 November 2013. http://dx.doi.org/10.1016/j.physio.2013.09.007

2- Al Rashoud AS, Abboud RJ, Wang W, Wigderowitz C (2012). The efficacy of low level laser therapy (LLLT) in the treatment of osteoarthritis of the knee, poster presented at the 15$^{TH}$ world congress of pain clinicians, Granada, Spain, 27 – 30 June 2012.

3- Participation in the international symposium on laser surgery held at the Security Forces Hospital, Riyadh, kingdom of Saudi Arabia, 5 – 7 October 2010.

4- Attending a low level laser therapy workshop held at the Security Forces Hospital, Riyadh, Kingdom of Saudi Arabia, January 3, 2011.

5- Attending a THOR laser therapy course on the application of LLLT and LED therapy, the physiological mechanisms, clinical applications, dosage, treatment techniques, safety and contraindications, London, UK, 18th July, 2010.